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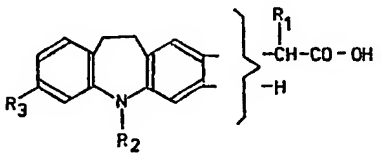
(54) PROCESS FOR THE PRODUCTION OF NEW DERIVATIVES OF 5H-DIBENZ[B,F]AZEPINE

(71) We, J. R. GEIGY A.G., a body corporate organised according to the laws of Switzerland, of 215, Schwarzwaldallee, Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention concerns processes for the production of new derivatives of 5H-dibenz[b,f] azepine and salts thereof, these new substances as well as new pharmaceutical preparations and use thereof.

Compounds of the general formula I,



(I)

wherein

R_1 represents hydrogen or a lower alkyl group with at most 3 carbon atoms,

R_2 represents hydrogen or a lower alkyl group with at most 4 carbon atoms and

R_3 represents hydrogen or chlorine,

as well as the pharmaceutically acceptable salts of the carboxylic acids, which are embraced by the general formula I, with inorganic and organic bases have not been described hitherto.

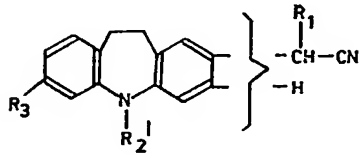
It has now been found that these new substances possess therapeutically valuable properties. They exhibit, in particular, an anti-inflammatory and anti-oedematous, analgesic and anti-pyretic action with favourable therapeutic index and, advantageously, they have only slight gastrointestinal secondary effects. The analgesic and anti-phlogistic activity of the compounds of the general formula I and of the salts of the carboxylic acids, embraced by this general formula, with inorganic and organic bases can be shown by various standard test methods. As a method for demonstrating the analgesic activity, reference is made to the "writhing test" described by E. Siegmund, R. Cadmus and G. Lu, Proc. Soc. Exp. Biol. Med. 95, 729 (1957). In this test, the amount of the test substances, which can be administered orally or parenterally, required to prevent the syndrome produced on mice by the intraperitoneal injection of 2-phenyl-1,4-benzoquinone is determined. The antiphlogistic activity is shown, for example, by the effect of the test substances with regard to reducing swelling after oral or parenteral adminis-

[Price 25p]

tration in the case of the bolus-albuminedum of the rat's paw, corresponding to the method described by G. Wilhelmi, Jap. J. Pharmacol. 15, 187 (1965). The new substances according to the invention can be used orally, rectally or parenterally, especially intramuscularly, for the therapy of rheumatic, arthritic and other inflammatory diseases. Moreover, the compounds of the general formula I and their salts are suitable as UV-absorbers for cosmetic purposes, e.g. as constituents of creams for protection against the sun.

In the compounds of the general formula I and in the corresponding starting materials given below, a lower alkyl group R_1 is, e.g. the methyl, ethyl or n-propyl group. As lower alkyl group, R_2 is, e.g. the methyl, ethyl, n-propyl, n-butyl or isobutyl group.

To produce the new compounds of the general formula I and their pharmaceutically acceptable salts with inorganic or organic bases salts, a compound of the general formula II,



(II)

wherein

R_2' represents hydrogen, a lower alkyl group having at most 4 carbon atoms, the benzyl group or a lower alkanoyl group having at most 4 carbon atoms and

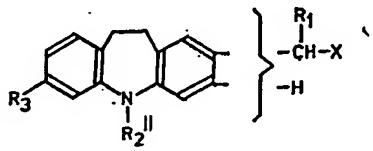
R_1 and R_3 have the means giving under formula I, is subjected to alcoholysis with a lower alkanol having at most 6 carbons atoms, the obtained alkyl ester is hydrolysed in an alkaline or acid medium and, when required, the carboxylic acid is liberated from a salt thereof with a base thus produced, and/or a free carboxylic acid or salt thereof with a base thus obtained is converted into, or into another, pharmaceutically acceptable salt thereof with a base.

The alcoholysis of the nitriles of the general formula II is performed by the simultaneous or successive action of a mineral acid, a lower alkanol and, optionally, water. For example, a nitrile of the general formula II is reacted with a mixture of hydrogen chloride and a lower alkanol in the presence or absence of an additional organic solvent such as, e.g. ether, whereby, by way of the imido chloride, the corresponding imidoalkylester hydrochloride is formed, which can be decomposed with water to give the corresponding lower alkyl ester. Optionally, a benzyl group R_2' can be split off in the course of the alcoholysis.

The hydrolysis of the aforementioned lower alkyl esters to give the corresponding carboxylic acids of the general formula I and/or their pharmaceutically acceptable salts with bases, is performed, for example, by boiling in an alkanolic aqueous alkali metal hydroxide solution.

The production of the nitriles of the general formula II, which are required as starting materials, is further dealt with below.

The free carboxylic acids embraced by the general formula I, and their pharmaceutically acceptable salts with inorganic or organic bases, are produced according to a second process which comprises hydrolysing, in an alkaline or acid medium, a compound of the general formula III,



(III)

wherein

X represents a group which can be hydrolysed to obtain the carboxylic group, especially the cyano group, a carboxylic acid imido ester group, a carboxylic acid ester group, the carbamoyl group, or a thiocarbamoyl group which can be mono- or di- alkyl substituted at the nitrogen atom, whereby in the case of di-substitution, the two alkyl groups can be bound by way of an oxygen atom,

R_2'' represents hydrogen, a lower alkyl group having at most 4 carbon atoms, a lower alkanoyl group having at most 4 carbon atoms, and

R_1 and R_3 have the meaning given under formula I, and, when required, liberating the free carboxylic acid from a salt thereof with a base thus produced, and/or converting a free carboxylic acid or a salt thereof with a base thus obtained into, or into another pharmaceutically acceptable salt thereof with a base.

For example, a carboxylic acid ester or carboxylic acid imido ester embraced by the general formula III is hydrolysed by boiling in an alkanolic-aqueous alkali metal hydroxide solution. The hydrolysis of corresponding nitriles, amides, thioamides or thiomorpholides is carried out, for example, in the same manner or by heating with a mineral acid, such as, e.g. concentrated hydrochloric acid, aqueous sulphuric acid or anhydrous phosphoric acid. More energetic conditions are used if, simultaneously with the hydrolysis of the group X, a lower alkanoyl group R_2'' is to be split off. The alkaline hydrolysis of a carboxylic acid derivative and

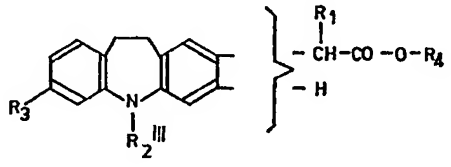
simultaneous splitting off of an alkanoyl radical R_2'' is performed, for example, with the aid of an alkali metal hydroxide in a solvent having a higher boiling point and containing hydroxyl groups, such as ethylene glycol.

The nitriles embraced by the general formula III, are produced in various ways which, in particular, depend on the position of the side chain and on the meaning of R_1. From 5 - acetyl - 3 - amino - 10,11 - dihydro - 5H - dibenz[b,f]azepines, optionally substituted according to the definition for R_3, are obtained by means of the Sandmeyer reaction the corresponding 5 - acetyl - 10,11-dihydro - 5H - dibenz[b,f]azepine - 3-carbonitriles. These compounds are converted by means of hydrolysis using alkali metal hydroxides in ethylene glycol or diethylene glycol at 150—200°C into corresponding 10, 11 - dihydro - 5H - dibenz[b,f]azepine - 3-carboxylic acids which, optionally, are then alkanoylated in 5-position. The 5 - acetyl-10,11 - dihydro - 5H - dibenz [b,f]azepine-3 - carboxylic acids or -2-carboxylic acids and their derivatives substitued according to the definition for R_3 can, if desired, also be produced from optionally accordingly substituted 3,5 - diacetyl - 10,11 - dihydro - 5H-dibenz[b,f]azepines and 2,5 - diacetyl - 10, 11 - dihydro - 5H - dibenz[b,f])azepines, respectively, the production of which is described below, by means of oxidation, e.g. using aqueous sodium hypochlorite solution in dioxane. The obtained carboxylic acids are reduced with diborane in an ethereal solvent to corresponding 10,11-dihydro-5H-dibenz-[b,f]azepine-3-methanols and -2-methanols respectively, or, with the presence of a 5-alkanoyl group in the starting material, to corresponding 5 - alkyl - 10,11 - dihydro-5H - dibenz[b,f]azepine - 3 - methanols and -2-methanols respectively. 10,11 - Dihydro-5H - dibenz[b,f]azepine - 2 - methanol and its derivatives substituted according to the definition for R_2'' and R_3, can also be obtained by reduction of a methyl ester derived from one of the aforementioned carboxylic acids with lithium aluminium hydride in an etherial solvent or by reduction or hydrogenation of the corresponding 10,11 - dihydro - 5H - dibenz[b,f]azepine - 2 - carboxaldehydes, the production of which is described below.

The hydroxy compounds thus obtained in various ways are converted either in the usual manner, e.g. using phosphorus tribromide, phosphorus pentachloride or thionyl chloride, into corresponding bromine or chlorine compounds, or they are firstly converted into their alkali metal compounds, which are then reacted with sulphonic acid halides, e.g. with *p*-toluene sulphonic acid chloride, to give corresponding sulphonic acid esters. The stated bromine, chlorine or sulphonyloxy compounds are now reacted with alkali metal cyanides to give the nitriles which are embraced by the general formula III.

Optionally, other functional derivatives of these acids, which can likewise be hydrolysed, and in some cases more easily so, to give free acids of the general formula I, are produced in the usual manner from the nitriles. The conversion of the nitriles into imidoalkyl ester hydrochlorides and hydrolysis of the latter to give corresponding lower alkyl esters, which are also embraced by the general formula I, has already been mentioned. Amides, covered by the general formula III, are obtained, for example, by the action of hydrogen peroxide on the corresponding nitriles in aqueous acetone or aqueous lower alkanols at temperatures of 40—60°.

The N-alkylated esters, as starting materials, are obtained by reacting cold, in an ethereal solvent, e.g. a compound of the general formula IIIa,



(IIIa)

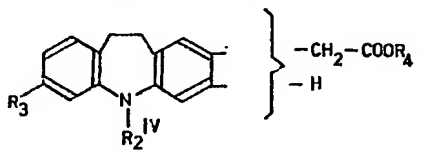
wherein

R_2''' represents a lower alkanoyl group having at most 4 carbon atoms and

R_4 represents a lower alkyl group having at most 4 carbon atoms,

and R_1 and R_3 have the meaning given under formula I, with diborane. Suitable as the reaction medium are, e.g. tetrahydrofuran, diethylether, dioxane, methylene glycol dimethylether or diethylene glycol dimethylether. The reaction temperature is preferably between −30° and room temperature. The diborane is formed, e.g. from boron trifluoride etherate and sodium boron hydride either in a separate apparatus and introduced into the reaction mixture, or it is formed in situ.

The α-C-alkylated esters, as starting materials, are obtained by reacting a compound of the general formula IIIb



(IIIb)

wherein,

R_3 and R_1 have the meaning given under formula IIIa and

R_2^{IV} represents a lower alkyl group having at most 4 carbon atoms or a lower

alkanoyl group having at most 4 carbon atoms,

in the presence of the essentially equimolar amount of an alkaline condensation agent in a suitable solvent such as, e.g. hexamethyl phosphoric acid triamide or dimethyl formamide, with an essentially equimolar amount of a reactive ester of a hydroxy compound of the general formula IV,

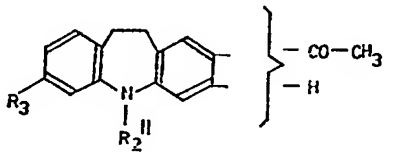
$$R_1'—OH \qquad (IV)$$

wherein R_1' has the meaning given under formula I for R_1, with the exception of hydrogen. Compounds of the general formula IIIb, wherein

R_2^{IV} represents a lower alkanoyl group having at most 4 carbon atoms,

are hydrolysed in an alkaline medium, whereby splitting off of the alkanoyl group occurs.

Thioamides, mono- and di-substituted thioamides and, in particular, thiomorpholides of carboxylic acids of the general formula I, wherein R_1 is hydrogen, all corresponding to the general formula III, are produced starting with compounds of the general formula IIIc,



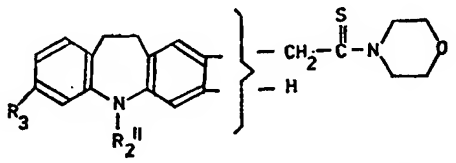
(IIIc)

wherein

R_2'' represents hydrogen, a lower alkyl group with at most 4 carbon atoms or a lower alkanoyl group having 1—4 carbon atoms, and

R_3 has the meaning given under formula I,

using the methods of Willgerodt or Willgerodt-Kindler. According to these methods, a compound of the general formula IIIc is heated with ammonium polysulphide, or with ammonia or a primary or secondary amine and sulphur. The reaction of a compound of the general formula IIIc with ammonium polysulphide is, for example, performed in a medium in which one, or preferably both, reactants are at least partially soluble such as, e.g. dioxane, in a closed vessel at temperatures around 160—220°C. According to Kindler's modification, a compound of the general formula IIIc can, for example, be reacted with aqueous or anhydrous ammonia, or with a lower mono- or dialkylamine containing at most 6 carbon atoms or piperidine and with sulphur, likewise in a closed vessel and, optionally, in the presence of pyridine at temperatures of 140—180°C. According to the most common embodiment of the Kindler modification, morpholine is used as amine, whereby its boiling point of 138°C renders unnecessary the use of pressure vessels. For example, the compound of the general formula IIIc and sulphur are refluxed in excess morpholine for some time, e.g. about 5—40 hours. The morpholide of a thio acid, embraced by the general formula III and defined by formula IIId,



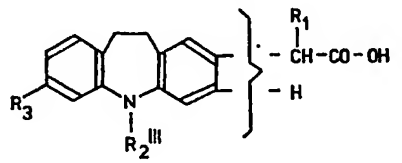
(IIId)

wherein R_2'' and R_3 have the meaning given under formula III, is likewise hydrolysed like the thioamides obtained in the case of the other embodiments, e.g. by boiling with alkanolic or alkanolic-aqueous potassium or sodium hydroxide solution. Of the compounds required as starting materials for the Willgerodt reactions and Willgerodt-Kindler reactions, the 3,5-diacetyl-10,11-dihydro-5H-dibenz[b,f]azepine and the 3-acetyl-10,11-dihydro-5H-dibenz[b,f]azepine are known. Analogously to these known compounds, compounds having a substituent R_3, as defined, are produced by condensation of correspondingly substituted 5-acetyl-10,11-dihydro-5H-dibenz[b,f]azepines with acetyl chloride according to the Friedel-Crafts reaction and, optionally, subsequent hydrolysis to split off the 5-acetyl group. From the 3-acetyl compounds unsubstituted in 5-position, compounds are obtained with other lower alkanoyl groups or with lower alkyl groups as substituent R_2'' by alkanoylation with formic acid/acetic acid anhydride mixtures, or with acetyl chlorides, propionyl chloride or butyryl chloride, or by reacting with lower alkyl halides, such as methyl iodide, at increased temperatures, e.g. in methanol solution in a closed vessel.

The compounds of the general formula IIIc substituted in 2-position by the acetyl group, whereby R_3 has the meaning given under formula III and R_2'' denotes a lower alkyl group having 1—4 carbon atoms, are produced by reacting a 5-alkyl-10,11-dihydro-5H-dibenz[b,f]azepine with N,N-dimethyl formamide and phosphorus oxychloride using the Vilsmeier method, to give the correspondingly substituted 5 - alkyl - 10,11 - dihydro - 5H - dibenz[b,f]azepine - 2 - carboxaldehyde, converting this, in a known manner, into the 5 - alkyl - 10,11 - dihydro - 5H-dibenz[b,f]azepine - 2 - carboxaldoxime. The latter is converted by heating with acetic acid anhydride into the 5 - alkyl - 10,11 - dihydro - 5H - dibenz[b,f]azepine - 2 - carbonitrile, which is converted by means of a Grignard reaction and in a known manner,

into the 2 - acetyl - 5 - alkyl - 10,11 - dihydro - 5H - dibenz[b,f]azepine of the general formula IIIc.

Compounds of the general formula I, wherein R_2 denotes hydrogen, whilst R_1 and R_3 have the meaning given under formula II, and pharmaceutically acceptable salts thereof with bases are produced by a third process which comprises hydrolysing a compound of the general formula V,



(V)

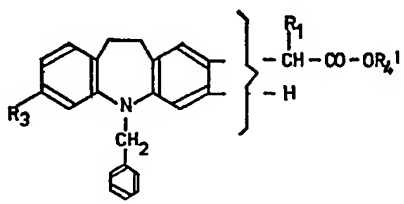
wherein

R_2''' represents a lower alkanoyl group having at most 4 carbon atoms, and

R_1 and R_3 have the meaning given under formula I, in an alkaline or acid medium and, when required, liberating the free carboxylic acid from a salt thereof with a base thus produced, and/or converting a free carboxylic acid or a salt thereof with a base thus obtained into, or into another, pharmaceutically acceptable salt thereof with a base.

The hydrolysis is performed in the usual manner, e.g. by heating the compounds of the general formula V with aqueous-organic or organic alkali hydroxide solutions or with mineral acids. In general however, more energetic reaction conditions are necessary than, e.g. for the hydrolysis of alkyl esters embraced by the general formula III. The hydrolysis is therefore carried out preferably at high temperatures, either in a closed vessel or in a medium having a higher boiling point such as, e.g. ethylene glycol, at the boiling point of the latter. As already mentioned, the hydrolysis of a compound of the general formula III to give the corresponding free acid, or a salt thereof, and the splitting off of a lower alkanoyl group present in 5-position, can also be carried out in the same operation.

The same types of compounds of the general formula I, as obtained using the third mentioned process, are produced by a related fourth production process, which comprises reacting a compound of the general formula VI,



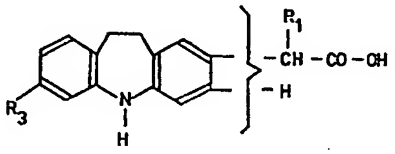
wherein

R_1 and R_3 have the meaning given under formula I, and

R_4' represents hydrogen, a lower alkyl group having at most 6 carbon atoms or the benzyl group,

with a saturated solution of a hydrohalic acid, preferably a hydrobromic acid, at an elevated temperature, or when R_4' represents a benzyl group, with catalytically activated hydrogen and, when required, converting a free carboxylic acid thus obtained into a pharmaceutically acceptable salt with a base. For example, a compound of the general formula VI is heated with saturated, aqueous hydrobromic acid at temperatures between about 80° and boiling temperature. The catalytic hydrogenolysis to split off the benzyl radical is performed, for example, in the presence of noble metal catalysts or Raney-nickel in suitable organic solvents, such as ethanol or dioxane, at normal or moderately increased pressure and likewise temperature. As already mentioned above, the splitting off of the benzyl group by means of hydrobromic acid can also be carried out in the same operation as the acid hydrolysis of a suitable compound of the general formula III.

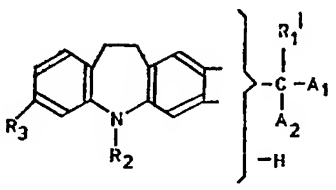
According to a fifth process, compounds of the general formula I, wherein R_2 is different to hydrogen, are produced by reacting a compound of the narrower general formula VII,



(VII)

which is embraced by the general formula I and whereby, in formula VII, R_1 and R_3 have the meaning given under formula I, with a reactive ester of a lower alkanol having at most 4 carbon atoms and, when required, converting thus obtained free carboxylic acid into a pharmaceutically acceptable salt with an inorganic or organic base. For example, a compound of the general formula VII is heated in an organic solvent such as, e.g. chloroform, benzene, toluene or methanol, if necessary in a closed vessel, with a lower alkyl halide such as methyl or ethyl iodide, or methyl or ethyl chloride.

According to a sixth process, compounds of the general formula I, wherein R_1 represents an alkyl group having at most 3 carbon atoms, and their pharmaceutically acceptable salts with bases are obtained by reacting a compound of the general formula VIII,



(VIII)

wherein

R_1' represents an alkyl group having at most 3 carbon atoms,

A_1 represents a lower alkoxycarbonyl group (—CO—O—alkyl) having at most 6 carbon atoms or the cyano group and

A_2 represents a lower alkoxycarbonyl group having at most 6 carbon atoms, a lower alkoxalyl group

(—CO—CO—O—alkyl),

having at most 7 carbon atoms, the cyano group or the acetyl group, and

R_2 and R_3 have the meaning given under formula I, with an alkali metal hydroxide in an organic or organic-aqueous medium or, when neither A_1 nor A_2 is a cyano group, with an alkali metal alkanolate in an anhydrous medium or, when A_2 is not an acetyl radical, with a mineral acid in an organic-aqueous medium, liberating the free acid from any salt thereof obtained on use of an alkali metal hydroxide and heating said dicarboxylic acid until the equimolar amount of carbon dioxide or carbon monoxide has been split off, and, when required, liberating the free carboxylic acid from a salt thereof with a base thus produced, and/or converting a free carboxylic acid or a salt thereof with a base thus obtained into, or into another, pharmaceutically acceptable salt thereof with a base.

The reactions with alkali metal hydroxides, especially sodium or potassium hydroxide, are preferably performed hot. Suitable as a reaction medium are, e.g. a lower alkanol containing at most 4 carbon atoms, such as methanol, ethanol, isopropanol or n-butanol, also an alkane diol or a monoalkylether thereof, e.g. ethylene glycol, 2-methoxy ethanol or 2-ethoxy ethanol, whereby, optionally, water in the volume ratio of ca. 10:1 to 1:2 is added to the stated solvents. Moreover, as a reaction medium, it is also possible to use water or, e.g. a mixture of water with water-soluble ethereal solvents, such as dioxane or tetrahydrofuran.

Whereas in the case of the reaction with alkali metal hydroxides under energetic reaction conditions, e.g. in a boiling mixture of ethylene glycol or n-butanol with a little water, in the aforementioned process, direct salts of monocarboxylic acids of the general formula I are formed; salts of dicarboxylic acids are, optionally, firstly obtained under less energetic conditions, e.g. in methanol or ethanol. From these salts are then liberated, according to the process, the corresponding dicarboxylic acids and the latter are subsequently decomposed to compounds of the general formula I.

Starting materials of the general formula VIII are produced, for example, starting with compounds of the general formula III, wherein X denotes a lower carboxylic acid alkyl ester group (lower alkoxycarbonyl group) or the cyano group, R_1 represents hydrogen, R_2 represents hydrogen or a lower alkyl group and R_3 denotes hydrogen or chlorine. Such like lower alkyl esters, or nitriles, are condensed with lower dialkyl carbonates, lower oxalic acid dialkyl esters or acetic acid alkyl esters with the aid of alkali metal alkanolates in lower alkanols or, for example, also in inert organic solvents such as benzene or toluene, and the alkali metal compounds of the obtained condensation products, to introduce the alkyl group R_1', are reacted with alkyl halides having at most 3 carbon atoms.

The new compounds of the general formula I and the pharmaceutically acceptable salts of the carboxylic acids, embraced by this formula, with inorganic and organic bases can be administered, as already mentioned, orally, rectally or parenterally, in particular, intramuscularly. They can, however, also be used externally in foundations for ointments and sun-protection oils.

Suitable as salts for therapeutic application are those having pharmacologically acceptable inorganic and organic bases, i.e. bases which exhibit, in the dosages in question, no physiological inherent action or else a desired action, e.g. having, for example, in the case of perenteral forms of administration, in particular a local anaesthetic action. Suitable salts are, e.g. sodium, potassium, lithium, magnesium, calcium and ammonia salts, also salts with ethylamine, triethylamine, ethanolamine, diethanolamine, 2-dimethylamino-ethanol, 2-diethylamino-ethanol, ethylene diamine, benzyl amine, procaine, pyrrolidine, piperidine, morpholine, 1-ethyl-piperidine or 2-piperidino-ethanol.

In a further aspect therefore, the present invention provides a pharmaceutical composition comprising a compound of formula I as defined above, or a pharmaceutically acceptable salt thereof with a base together with a pharmaceutically acceptable diluent or carrier therefor.

The daily dosages, to be taken internally, of compounds of the general formula I, or of pharmacologically acceptable salts of such compounds with bases, for the treatment of rheumatic, arthritic and other inflammatory diseases are between 2—15 mg/kg, preferably 5—10 mg/kg for adult patients. Suit-

able dosage units such as dragees, tablets, suppositories or ampoules, preferably contain 10—250 mg of a compound of the general formula I, or of a pharmaceutically acceptable salt of a carboxylic acid embraced by the general formula I with a base.

Dosage units for oral administration contain as active substance preferably between 10% and 90% of a compound of the general formula I or of a pharmacologically acceptable salt of a carboxylic acid embraced by this formula with a base. They are produced by combining the active substances with e.g. solid, pulverulent carriers such as lactose, saccharose, sorbitol, mannitol; starches such as potato starch, maize starch or amylopectin, also laminaria powder or citrus pulp powder; cellulose derivatives or gelatine, optionally with the addition of lubricants such as magnesium or calcium stearate or polyethylene glycols having suitable molecular weights, to form tablets or dragée cores. The latter are coated, for example, with concentrated sugar solutions which can also contain, e.g. gum arabic, talcum and/or titanium dioxide, or with a lacquer dissolved in easily volatile organic solvents or mixtures of solvents. Dyestuffs can be added to these coatings, e.g. to indicate varying dosages of active substance.

Prescriptions

The following prescriptions describe in more detail the production of tablets and dragees:

a) 1000.0 g of active substance are mixed with 550.0 g of lactose and 292.0 g of potato starch. The mixture is moistened with an alcoholic solution of 8.0 g of gelatine and is granulated through a sieve. After drying, 60.0 g of potato starch, 60.0 g of talcum, 10.0 g of magnesium stearate and 20.0 g of colloidal silicon dioxide are mixed in. The mixture is then compressed into 10,000 tablets each weighing 20 mg and each containing 100 mg of active substance. Optionally, the tablets can be provided with grooves for more accurate adjustment of the dosage amount.

b) 200.0 g of active substance are well mixed with 16 g of maize starch and 6.0 g of colloidal silicon dioxide. The mixture is moistened with a solution of 2.0 g of stearic acid, 6.0 g of ethyl cellulose and 6.0 g of stearin in ca. 70 ml of isopropyl alcohol and is then granulated through a sieve III (Ph. Helv. V). The granulate is dried for ca. 14 hours and then put through sieve III—IIIa. The granulate is then mixed with 16.0 g of maize starch, 16.0 g of talcum and 2.0 g of maize starch, 16.0 g of talcum and 2.0 g of magnesium stearate and the mixture is compressed into 1000 dragee cores. These are coated with a concentrated syrup made from 2000 g of lacca, 7,500 g of gum arabic, 0.150 g of dyestuff, 2000 g of highly dispersed silicon dioxide, 25,000 g of talcum and 53,350 g of sugar, and dried. The obtained dragees each weigh 360 mg and each contain 200 mg of active substance.

Suitable dosage units for rectal administration are, e.g. suppositories which consist of a combination of a compound of the general formula I, or of a suitable salt of a carboxylic acid embraced by the general formula I, with a neutral fatty foundation, or also gelatine rectal capsules which contain a combination of an active substance, or of a suitable salt thereof, with polyethylene glycols.

Ampoules for parenteral, particularly intramuscular administration, preferably contain a water soluble salt, e.g. sodium salt, of a carboxylic acid embraced by the general formula I, in a concentration preferably of 0.5—5% in aqueous solution, optionally together with suitable stabilisers and buffer substances.

The following examples further illustrate the carrying out of the process according to the invention without in any way limiting the scope of the invention. Temperatures are given in degrees Centrigrade.

EXAMPLE 1

5 - methyl - 10,11 - dihydro - 5H - dibenz-[b,f]azepine - 3 - acetic acid

A solution of 10.0 g of 5 - methyl - 10,11-dihydro - 5H - dibenz[b,f] - 3 - acetonitrile in 500 ml of chloroform and 50 ml of absolute ethanol is saturated at 0—5° with hydrogen chloride and then stirred for 14 hours at 20—25°. The solution is then concentrated by evaporation, the residue is stirred with 100 ml of dioxane and 20 ml of water at 40° for 5 hours and again concentrated by evaporation. The crude ethyl ester is refluxed for one hour with 100 ml of ethanol and 30 ml of 5N sodium hydroxide solution. The ethanol is distilled off and the remaining alkaline solution is acidified with 2N hydrochloric acid. The obtained aqueous suspension is extracted with ethyl acetate and the organic phase is then repeatedly extracted with 2N sodium carbonate solution. The sodium carbonate solutions are combined and acidified with 2N hydrochloric acid. The precipitated pale yellow crystals are filtered by suction and recrystallised from cyclohexane. The 5 - methyl - 10,11 - dihydro-5H - dibenz[b,f]azepine - 3 - acetic acid, M.P. 140—141°, is obtained.

5 - butyl - 10,11 - dihydro - 5H - dibenz-[b,f]azepine - 3 - acetic acid (oil) is obtained analogously, starting with 7.8 g of 5 - butyl-10,11 - dihydro - 5H - dibenz[b,f] azepine-3 - acetonitrile (oil).

The starting materials are produced as follows:

a) 10,11 - dihydro - 5H - dibenz[b,f]azepine-3 - carboxylic acid.

16.5 g of 5 - acetyl - 10,11 - dihydro - 5H-dibenz[b,f]azepine - 3 - carboxylic acid are refluxed in a solution of 15.0 g of potassium hydroxide in 300 ml of absolute ethanol for 16 hours. After cooling, the ethanol is completely evaporated in a rotary evaporator and the residue is dissolved in water. The clear aqueous phase is acidified and the precipitated crystals are filtered by suction and recrystallised from absolute ethanol, whereby the 10,11 - dihydro - 5H - dibenz[b,f]-azepine - 3 - carboxylic acid is obtained, M.P. 196—197°.

b_1) 5 - formyl - 10,11 - dihydro - 5H - dibenz[b,f]azepine - 3 - carboxylic acid.

70 ml of acetic anhydride are mixed at 35—40° with 35 ml of formic acid. After one hour, 11 g of 10,11-dihydro-5H-dibenz-[b,f]azepine-3-carboxylic are introduced into the solution at 45—50° within 1 1/2 hours. The mixture is then stirred for a further 2 1/2 hours at 45—50° and for 8 hours at 20—25°. 100 ml of water are then added dropwise at 40—50° and, after cooling, the precipitated crystals are filtered by suction. The 5 - formyl - 10,11 - dihydro - 5H - dibenz[b,f]azepine - 3 - carboxylic acid, after recrystallisation from ethanol, melts at 226—228°.

b_2) The corresponding 5 - butyryl - 10,11-dihydro - 5H - dibenz[b,f]azepine - 3-carboxylic acid is produced as follows:

5 - butyryl - 10,11 - dihydro - 5H - dibenz-[b,f]azepine - 3 - carboxylic acid.

b) 3 - acetyl - 5 - butyryl - 10,11 - dihydro-5H - dibenz[b,f]azepine.

9.2 g of 5-butyryl-10,11-dihydro-5H-dibenz[b,f] azepine are dissolved in 50 ml of carbon disulphide and mixed with 3.43 g of acetyl chloride. 19 g of aluminium chloride are introduced, in portions, at 40° within 40 minutes. The mixture is refluxed for 1 hour and then mixed with 3.43 g of acetyl chloride. After refluxing for 15 hours, 50 ml of carbon disulphide, 1.5 g of acetyl chloride and 5 g of aluminium chloride are added and the mixture is refluxed for a further 20 hours. The carbon disulphide is now separated and the brown, resinous residue is triturated with a lot of ice and 5N hydrochloric acid. The suspension is extracted with ethyl acetate, the organic phase is washed with 2N sodium carbonate solution, dried and concentrated by evaporation. A colourless oil remain behind, which can be further used without purification.

30.7 g of 3 - acetyl - 5 - butyryl - 10,11-dihydro - 5H - dibenz[b,f]azepine are dissolved in 300 ml of dioxane and 100 ml of water and, while stirring, 240 ml of 11% aqueous sodium hypochlorite solution are added dropwise at 0° within 30 minutes. The reaction mixture is stirred firstly for 30 minutes at 0° and then for 2 hours at room temperature. The dioxane is then evaporated off in vacuo. The aqueous phase which remains behind is washed with ether and then acidified with concentrated hydrochloric acid. The precipitated crystals are filtered by suction, dried and recrystallised from benzene/cyclohexane. The thus obtained 5 - butyryl-10,11 - dihydro - 5H - dibenz[b,f]azepine-3 - carboxylic acid melts at 108—110°.

c) 5 - methyl - 10,11 - dihydro - 5H - dibenz[b,f]azepine - 3 - methanol.

9.5 g of the above 5-formyl-3-carboxylic acid are dissolved in 100 ml of freshly distilled absolute tetrahydrofuran. Within 1 1/2 hours at 8—12°, diborane is introduced, which is produced from 7 g of sodium boron hydride and 38.8 ml of boron trifluoride etherate in 230 ml of diethylene glycol dimethylether according to Organic Reactions 13, 31 (1963). The solution is stirred for a further 2 hours at 0—5° and then it is carefully mixed at −10° to 0° with 20 ml of water. The mixture is made acid with 2N hydrochloric acid and diluted with 500 ml of water. It is then extracted with ethyl acetate and the obtained organic phase is washed with 2N sodium carbonate solution. The ethyl acetate is evaporated off and a colorless oil is obtained which can be further processed without purification.

The following is produced in an analogous manner:

5 - n - butyl - 10,11 - dihydro - 5H - dibenz[b,f] azepine - 3 - methanol is obtained as a colorless oil, starting with 10.3 g of 5 - butyryl - 10,11 - dihydro - 5H - dibenz-[b,f] azepine - 3 - carboxylic acid, M.P. 108—110°.

d) 3 - bromomethyl - 5 - methyl - 10,11-dihydro - 5H - dibenz[b,f] azepine.

A solution of 8.5 g of the above product obtained under c) in 300 ml of chloroform is saturated at 0° with hydrogen bromide, stirred for 12 hours at 20—25° and then washed with 2N sodium carbonate solution. The organic phase is concentrated by evaporation, whereby the 3 - bromomethyl-5 - methyl - 10,11 - dihydro - 5H - dibenz-[b,f]azepine remains behind as a colorless oil.

The following is produced in an analogous manner:

3 - bromomethyl - 5 - butyl - 10,11 - dihydro - 5H - dibenz[b,f] azepine is obtained as a colorless oil, starting with 8.9 g of 5 - butyl - 10,11 - dihydro - 5H - dibenz-[b,f] azepine - 3 - methanol (oil).

e) 5 - methyl - 10,11 - dihydro - 5H - dibenz[b,f]azepine - 3 - acetonitrile.

12.7 g of the above bromine compound are stirred with 6.3 g of potassium cyanide in 100 ml of dimethyl sulphoxide for 5 hours at 40—50°, then poured on to ice and mixed with 500 ml of water. After extraction with a large amount of ether and evaporation of the solvent, the 5-methyl-10,11-dihydro-5H-

dibenz[b,f] azepine-3-acetonitrile is obtained as colorless crystals, M.P. 78—81° (from ethyl acetate).

5 - butyl - 10,11 - dihydro - 5H - dibenz-[b,f]azepine - 3 - acetonitrile (oil) is obtained analogously starting with 7.7 g of 3 - bromomethyl - 5 - butyl - 10,11 - dihydro - 5H-dibenz[b,f]azepine.

EXAMPLE 2

5,α - dimethyl - 10,11 - dihydro - 5H-dibenz[b,f]azepine - 3 - acetic acid.

A solution of 3.4 g of 5,α - dimethyl - 10, 11 - dihydro - 5H - dibenz[b,f]azepine - 3-acetonitrile in 170 ml of chloroform and 17 ml of absolute ethanol is saturated at 0.5° with hydrogen chloride and then stirred for 14 hours at 20—25°. The solution is then concentrated by evaporation, the residue is stirred with 35 ml of dioxane and 7 ml of water for 5 hours at 40° and again concentrated by evaporation. The crude ethyl ester is refluxed for one hour with 35 ml of ethanol and 10 ml of 5N sodium hydroxide solution. The ethanol is distilled off and the alkaline solution remaining behind is acidified with 2N hydrochloric acid. The obtained aqueous suspension is extracted with ethyl acetate and the organic phase is then repeatedly extracted with 2N sodium carbonate solution. The sodium carbonate solutions are combined and acidified with 2N hydrochloric acid. The precipitated, pale yellow crystals are filtered by suction and recrystallised from cyclohexane. The 5,α - dimethyl - 10,11-dihydro - 5H - dibenz[b,f] azepine - 3-acetic acid, M.P. 138-140° (from benzene) is obtained.

The starting material for the above example is produced as follows:

a) 3 - acetyl - 5 - formyl - 10,11 - dihydro-5H - dibenz[b,f] azepine.

70 ml of acetic anhydride are mixed at 35—40° with 35 ml of formic acid. After one hour, 10 g of 3 - acetyl - 10,11 - dihydro-5H - dibenz[b,f]azepine are added to the solution at 45—50° within 1 1/2 hours. The mixture is then stirred for 2 1/2 hours at 45—50°. 100 ml of water are then slowly added dropwise at 45—50°. After cooling, the mixture is extracted with ethyl acetate. The 3 - acetyl - 5 - formyl - 10,11 - dihydro-5H - dibenz[b,f]azepine, after recrystallisation from benzene/petroleum ether, melts at 111—113°.

b) 5,α - dimethyl - 10,11 - dihydro - 5H-dibenz[b,f]azepine - 3 - methanol.

7.3 g of the above 3-acetyl-5-formyl compound are dissolved in 100 ml of freshly distilled absolute tetrahydrofuran. Diborane is introduced at 8—12° with 1 1/2 hours. The diborane is produced from 7 g of sodium boron hydride and 38.8 ml of boron trifluoride etherate in 230 ml of diethylene glycol dimethyl ether according to Organic Reactions 13, 31 (1963). The solution is further stirred for 2 hours at 0—5° and then carefully mixed at −10 to 0° with 20 ml of water. The mixture is rendered acid with 2N hydrochloric acid and is diluted with 500 ml of water. It is then extracted with ethyl acetate and the obtained organic phase is washed with 2N sodium carbonate solution. With evaporation of the ethyl acetate, the 5,α - dimethyl - 10,11 - dihydro - 5H-dibenz[b,f]azepine - 3 - methanol remains behind as a colorless oil, which can be further processed without purification.

c) 3 - (1 - bromethyl) - 5 - methyl - 10,11-dihydro - 5H - dibenz[b,f]azepine.

A solution of 3.1 g of the above reduction product in 100 ml of chloroform is saturated at 0° with hydrogen bromide. The solution is stirred for 12 hours at 20—25° and then washed with 2N sodium carbonate solution. The organic phase is concentrated by evaporation, whereby the 3 - (1 - bromethyl)-5 - methyl - 10,11 - dihydro - 5H - dibenz-[b,f]azepine remains behind as a colorless oil.

d) 5,α - dimethyl - 10,11 - dihydro - 5H-dibenz[b,f]azepine - 3 - acetonitrile.

2.5 g of the above bromine compound are stirred with 1.3 g of potassium cyanide in 20 ml of dimethyl sulphoxide for 5 hours at 40—50° and then poured on to ice and mixed with 120 ml of water. After extraction with a lot of ether and evaporation of the solvent, the 5,α - dimethyl - 10,11 - dihydro-5H - dibenz[b,f]azepine - 3 - acetonitrile is obtained as oil.

EXAMPLE 3

10,11 - dihydro - 5H - dibenz[b,f]azepine-2 - acetic acid.

A solution of 6 g of 5 - benzyl - 10,11-dihyro - 5H - dibenz[b,f]azepine - 2 - acetonitrile in 90 ml of absolute ether and 60 ml of absolute ethanol is cooled, while stirring and with the exclusion of moisture, to 5°. Dry hydrogen chloride is introduced into the solution during 3 hours, whereby the temperature has not to exceed 5°. During a further 5 hours, hydrogen chloride is introduced into the solution at room temperature. The solution is then allowed to stand for 15 hours at room temperature and is then evaporated to dryness under 11 Torr at 40°. The residue is dissolved in 20 ml of water, the solution is covered with 40 ml of ether and the whole is refluxed on the water bath for 1 1/2 hours. The mixture is then cooled, the ether phase is separated and the aqueous solution is again extracted with 30 ml of ether. The combined ether solutions are dried over magnesium sulphate and concentrated by evaporation under 11 Torr at 40°.

The crude 10,11 - dihydro - 5H - dibenz-[b,f]azepine - 2 - acetic acid ethyl ester which remains behind is dissolved in 200 ml

of ethanol and 50 ml of 2N sodium hydroxide solution. The solution is refluxed for 3 hours and concentrated by evaporation to dryness under 11 Torr at 50°. The residue is dissolved in 100 ml of water and the aqueous solution is extracted with 50 ml of ether. The ethereal phase is separated and the aqueous phase acidified by the addition of 2N hydrochloric acid. The precipitated oil is dissolved in 100 ml of ether, the ethereal solution washed with 20 ml of water and dried over sodium sulphate. It is then concentrated under 11 Torr at 40°, whereby the 10,11 - dihydro-5H - dibenz[b,f]azepine - 2 - acetic acid crystallises out, M.P. 155—158°.

Obtained analogously is the 5 - methyl-10,11 - dihydro - 5H - dibenz[b,f]azepine-2 - acetic acid, M.P. 121—123° starting with 5 - methyl - 10,11 - dihydro - 5H - dibenz-[b,f] azepine - 2 - acetonitrile.

7 - chloro - 5 - methyl - 10,11 - dihydro-5H - dibenz[b,f] azepine - 2 - acetic acid, M.P. 175—187° is obtained analogously, starting with 7 - chloro - 5 - methyl - 10,11-dihydro - 5H - dibenz[b,f]azepine - 2-acetonitrile.

The nitrile required as starting material is produced as follows:

a_1) 5 - benzyl - 10,11 - dihydro - 5H - dibenz[b,f]azepine - 2 - carboxaldehyde.

61 g of distilled phosphorus oxychloride are added dropwise at 10° to 120 ml of dimethyl formamide within 10 minutes. The mixture is cooled to 0° and, while stirring well, a solution of 38 g of 5 - benzyl - 10.11-dihydro - 5H - dibenz[b,f]azepine (B.P. 178—181/0.15 Torr, M.P. 66—68° from ethanol, produced by condensation of 10,11-dihydro-5H-dibenz[b,f]azepine with benzyl chloride by means of sodium amide in boiling toluene) in 60 ml of dimethyl formamide is added dropwise within one hour at, at the most, 10°. The reaction mixture is then stirred for one hour at 70—75°. The dark orange coloured mixture is cooled and poured on to 500 g of ice, whereby the crude aldehyde precipitates as resin. The formed suspension is adjusted to pH 7 using concentrated sodium carbonate solution and then extracted with chloroform. The chloroform solution is washed with water, dried over calcium chloride and concentrated by evaporation in vacuo. The resin remaining behind is dissolved, while heating, in 350 ml of cyclohexane. The 5 - benzyl - 10,11-dihydro - 5H - dibenz[b,f]azepine - 2 - carboxaldehyde which crystallised upon cooling is filtered by suction, M.P. 99.5—101°.

a_2) The 5 - methyl - 10,11 - dihydro - 5H-dibenz[b,f]azepine - 2 - carboxaldehyde, M.P. 90—93° (from ethyl acetal/ether), is obtained starting with 5 - methyl - 10,11-dihydro - 5H - dibenz[b,f]azepine (M.P. 106—107° from ethanol, produced by condensation of 10,11-dihydro-5H-dibenz[b,f]-azepine with methyl iodide by means of sodium hydride in dimethyl formamide at 70°).

a_3) 7 - chloro - 5 - methyl - 10,11 - dihydro-5H - dibenz[b,f] azepine - 2 - carboxaldehyde is produced as follows:

330 g of phosphorus oxychloride are added dropwise to 700 ml of dimethyl formamide at 10° within 15 minutes. The mixture is cooled to 0° and, while stirring well, a solution of 150 g of 3 - chloro - 5 - methyl-10,11 - dihydro - 5H - dibenz[b,f]azepine (B.P. 170°/0.001 Torr, M.P. 56—58° from ethanol, produced by condensation of 3-chloro - 10,11 - dihydro - 5H - dibenz[b,f]-azepine with methyl iodide by means of sodium hydride in dimethyl formamide at 50°) in 700 ml of dimethyl formamide is added within one hour at a maximum temperature of 10°. The mixture is then stirred for two hours at 70°, cooled and poured on to 2000 g of ice, whereby the oil precipitates. By the addition of sodium carbonate, the mixture is adjusted to pH 7 and extracted with chloroform. The chloroform solution is washed with water, dried over calcium chloride and concentrated by evaporation in vacuo. The residue, a yellow oil, is a mixture of 7 - chloro - 5 - methyl-10,11 - dihydro - 10,11 - 5H - dibenz[b,f]-azepine - 2 - carboxaldehyde and 3 - chloro-5 - methyl - 10,11 - dihydro - 5H - dibenz-[b,f]azepine - 2 - carboxaldehyde.

b_1) 5 - Benzyl - 10,11 - dihydro - 5H - dibenz[b,f]azepine - 2 - methanol.

11.7 g of lithium aluminium hydride are suspended in 250 ml. of absolute ether and, while stirring, cooled to 5°. A solution of 50 g of 5 - benzyl - 10,11 - dihydro - 5H-dibenz[b,f]azepine - 2 - carboxaldehyde in 600 ml of absolute ether and 150 ml of absolute tetrahydrofuran are slowly added dropwise under nitrogen and with external cooling using an ice bath. The mixture is subsequently stirred for 18 hours at room temperature. It is then cooled to 5° and, while stirring, 12 ml of water, 12 ml of 15% sodium hydroxide solution and again 36 ml of water are added dropwise to the mixture. The latter is stirred for 2 hours at room temperature and then filtered. The filtrate is concentrated by evaporation under 11 Torr at 40° and the residue is distilled. The 5 - benzyl - 10,11 - dihydro - 5H - dibenz[b,f]azepine - 2 - methanol is obtained as a yellow oil. B.P. 190—200°/0.01 Torr.

b_2) The 5 - methyl - 10-11 - dihydro - 5H-dibenz[b,f]azepine - 2 - methanol, M.P. 78—79° (from ether/petroleum ether) is obtained analogously.

b_3) The 7 - chloro - 10,11 - dihydro - 5H-dibenz[b,f]azepine - 2 - methanol is obtained as follows:

70 g of lithium aluminium hydride are suspended in 900 ml of absolute ether and,

while stirring, cooled to 5°. To this is slowly added dropwise, under nitrogen and using an ice bath for external cooling, a solution of 165 g of a mixture consisting of 7 - chloro-5 - methyl - 10,11 - dihydro - 5H - dibenz-[b,f]azepine - 2 - carboxaldehyde and 3-chloro - 5 - methyl - 10,11 - dihydro - 5H-dibenz[b,f]azepine - 2 - carboxaldehyde (see a_2) in 500 ml of absolute ether and 300 ml of absolute tetrahydrofuran. The mixture is then stirred for 18 hours at room temperature. The mixture is cooled to 5° and, while stirring, 70 ml of water, 70 ml of 15% sodium hydroxide solution and a further 210 ml of water are added. The mixture is filtered and then washed with 300 ml of ether. The filtrate is concentrated by evaporation under 11 Torr at 40°. The residue, a mixture consisting of 7 - chloro - 5 - methyl - 10,11-dihydro - 5H - dibenz[b,f]azepine - 2-methanol and 3 - chloro - 5 - methyl - 10,11-dihydro - 5H - dibenz[b,f]azepine - 2-methanol, is chromatographed on 3000 g of neutral aluminium oxide. The fractions 25—28, eluted in each case with 3000 ml of ether, contain the approximately pure 7 - chloro-5 - methyl - 10,11 - dihydro - 5H - dibenz-[b,f] azepine - 2 - methanol as a yellowish oil.

c_1) 2 - bromomethyl - 5 - benzyl - 10,11-dihydro - 5H - dibenz[b,f] azepine.

A solution of 5 g of 5 - benzyl - 10,11-dihydro - 5H - dibenz[b,f]azepine - 2-methanol in 100 ml of chloroform is cooled to —5° using an ice/sodium chloride bath. While stirring, hydrogen bromide is introduced into the solution during an hour. The solution is then stirred during one hour at 0°. The mixture is poured on to 200 g of ice and the precipitated oil is extracted with 200 ml of ether. The ether solution is separated, extracted three times with 50 ml of 2N sodium carbonate solution and water, dried over magnesium sulphate and concentrated to dryness by evaporation under 11 Torr at 40°. The 2 - bromomethyl - 5-benzyl - 10,11 - dihydro - 5H - dibenz[b,f]-azepine remains behind as an oil and is directly further reacted.

c_1') 2 - chloromethyl - 5 - benzyl - 10,11-dihydro - 5H - dibenz[b,f]azepine.

A solution of 1.6 g of 5 - benzyl - 10,11-dihydro - 5H - dibenz[b,f]azepine - 2-methanol in 20 ml of absolute ether and 2 ml of absolute pyridine is quickly added dropwise to a solution, cooled to 0°, of 2 ml of thionyl chloride and 2 ml of pentane. The mixture is then stirred for one hour at 0° and then diluted with 10 ml of pentane. The mixture is extracted at 5°, twice in each case, with 10 ml of 1N hydrochloric acid, 10 ml of 1N sodium hydroxide solution and 10 ml of water. It is dried over potassium carbonate and concentrated to dryness under 11 Torr at 40°. The 2 - chloromethyl - 5-benzyl - 10,11 - dihydro - 5H - dibenz[b,f]-azepine is obtained as yellow oil.

The 2 - chloromethyl - 5 - methyl - 10,11-dihydro - 5H - dibenz[b,f]azepine is obtained as yellow oil in an analogous manner.

The 7 - chloro - 2 - chloromethyl - 5-methyl - 10,11 - dihydro - 5H - dibenz[b,f]-azepine (oil) is obtained analogously.

d_1) 5 - benzyl - 10,11 - dihydro - 5H - di-benz[b,f]azepine - 2 - acetonitrile.

A solution of 5 g of 2 - bromomethyl - 5-benzyl - 10,11 - dihydro - 5H - dibenz[b,f]-azepine (cf. c_1) in 20 ml of dimethyl sulphoxide is added, while stirring, to a suspension of 2.5 g of sodium cyanide in 30 ml of dimethyl sulphoxide at 40°. The mixture is then stirred for 15 hours at 40° and diluted with 400 ml of ice water. The solution is extracted four times with 200 ml of ethyl acetate. The ethyl acetate solutions are washed with 150 ml of 6N hydrochloric acid and then with 50 ml of water. They are subsequently dried with magnesium sulphate and concentrated by evaporation under 11 Torr at 40°. The residue is chromatographed on 200 g of neutral aluminium oxide. The fractions 3—6, eluted with ether, contain the 5 - benzyl - 10,11 - dihydro - 5H - dibenz-[b,f]azepine - 2 - acetonitrile, which when concentrated by evaporation, remains behind as yellow oil. The crude product is crystallised from ether, M.P. 96—98°.

The 5 - methyl - 10,11 - dihydro - 5H-dibenz[b,f]azepine - 2 - acetonitrile, M.P. 70—71° (from ether/petroleum ether) is obtained analogously from 2 - chloro - methyl-5 - methyl - 10,11 - dihydro - 5H - dibenz-[b,f]azepine.

7 - chloro - 5 - methyl - 10,11 - dihydro-5H - dibenz[b,f] azepine - 2 - acetonitrile, M.P. 117—119° (from methanol) is obtained analogously starting with 17 g of 7 - chloro-2 - chloromethyl - 5 - methyl - 10,11 - dihydro - 5H - dibenz[b,f] azepine (oil).

d_1') 5 - benzyl - 10,11 - dihydro - 5H - di-benz[b,f]azepine - 2 - acetonitrile.

The 5-benzyl-10,11-dihydro-5H-dibenz[b,f]azepine - 2 - acetonitrile is obtained analogously to example d_1) from 2 - chloromethyl - 5 - benzyl - 10,11 - dihydro - 5H-dibenz[b,f]azepine (cf. c_1')). The residue of the ethyl acetate solution is crystallised from ether, M.P. 96—98°, without a preceding chromatographic purification.

Example 4

10,11 - dihydro - 5H - dibenz[b,f]azepine-2 - acetic acid.

A solution of 1.2 g of 10,11 - dihydro-5H - dibenz[b,f]azepine - 2 - acetic acid methyl ester in 100 ml of ethanol and 15 ml of 2N sodium hydroxide solution is refluxed for 30 minutes and concentrated to dryness by evaporation under 11 Torr at 50°. The residue is dissolved in 50 ml of water and the

aqueous solution extracted with ether. The ethereal phase is separated and the aqueous phase is acidified by the addition of 2N hydrochloric acid. The precipitated crystals are filtered off, washed with a little water and dissolved in 40 ml of ether. The ethereal solution is dried over magnesium sulphate and concentrated under 11 Torr at 40°. The 10, 11 - dihydro - 5H - dibenz[b,f]azepine - 2-acetic acid crystallises out. After a single crystallisation from ether, it melts at 155—158°.

EXAMPLE 5

5 - methyl - 10,11 - dihydro - 5H - dibenz-[b,f]azepine - 3 - acetic acid.

0.9 g of crude 5 - methyl - 10,11 - dihydro - 5H - dibenz[b,f]azepine - 3 - acetic acid methyl ester are refluxed with 20 ml of ethanol and 7 ml of 5N sodium hydroxide solution for one hour. The ethanol is distilled off and the alkaline solution remaining behind is acidified with 2N hydrochloric acid. The formed, aqueous suspension is extracted with ethyl acetate, the organic phase is dried and concentrated by evaporation, whereby the 5-methyl - 10,11 - dihydro - 5H - dibenz[b,f]-azepine - 3 - acetic acid remains as yellow crystals, M.P. 140—141° after recrystallisation from cyclohexane.

The following is produced analogously:

5 - butyl - 10,11 - dihydro - 5H - dibenz-[b,f]azepine - 3 - acetic acid (oil) is obtained, starting with 1.3 g of crude 5 - butyl - 10, 11 - dihydro - 5H - dibenz[b,f] azepine - 3-acetic acid methyl ester.

The following is produced analogously:

α,5 - Dimethyl - 10,11 - dihydro - 5H-dibenz[b,f]azepine - 3 - acetic acid, M.P. 138—140°, starting with 1.2 g α,5 - dimethyl - 10,11 - dihydro - 5H - dibenz[b,f]-azepine - 3 - acetic acid methyl ester.

The starting materials can be produced as follows:

a) 10,11 - dihydro - 5H - dibenz[b,f]azepine-3 - acetic acid methyl ester.

2.0 g of 10,11 - dihydro - 5H - dibenz-[b,f]azepine - 3 - acetic acid are refluxed with 50 ml of absolute methanol and 200 mg of *p*-toluene sulphonic acid for 14 hours. The solvent is evaporated off under vacuum, the residue dissolved in ethyl acetate and the solution washed with 2N sodium carbonate solution. After evaporation of the ethyl acetate, the 10,11 - dihydro - 5H - dibenz[b,f]-azepine - 3 - acetic acid methyl ester remains behind as oil.

The α - methyl - 10,11 - dihydro - 5H-dibenz[b,f]azepine - 3 - acetic acid methyl ester is produced analogously.

b) 5 - formyl - 10,11 - dihydro - 5H - dibenz[b,f]azepine - 3 - acetic acid methyl ester.

10 ml of formic acid are added dropwise at 35° to 20 ml of acetic anhydride. The solution is stirred for one hour at 20—25° and then heated to 45°. 2.1 g of 10,11-dihydro - 5H - dibenz[b,f]azepine - 3-acetic acid methyl ester, dissolved in 6 ml of acetic anhydride, are added dropwise within 15 minutes. After stirring for 2 hours at 45—47°, the solution is mixed with 200 ml of water. It is allowed to stand for 2 hours and then extracted with ether. The ether solution is washed with 2N sodium carbonate solution and then concentrated by evaporation, whereby the 5 - formyl - 10,11 - dihydro - 5H - dibenz[b,f]azepine - 3 - acetic acid methyl ester remains behind. M.P. 85—87° (from ether).

The following is produced analogously:

5 - formyl - α - methyl - 10,11 - dihydro-5H - dibenz[b,f] azepine - 3 - acetic acid methyl ester (oil).

c) 1.5 g of 5 - formyl - 10,11 - dihydro - 5H-dibenz[b,f] azepine - 3 - acetic acid methyl ester are dissolved in 20 ml of freshly distilled absolute tetrahydrofuran. Diborane is introduced at −15 to −10° within 1 1/2 hours. The diborane is produced from 1.05 g of sodium boron hydride and 5.9 ml of boron trifluoride etherate in 34.5 ml of diethylene glycol dimethyl ether according to Organic Reactions 13, 31 (1963). The solution is further stirred for 2 hours at 0° and then at −10 to −5° carefully mixed with 3 ml of water. The mixture is rendered acid with 2N hydrochloric acid and diluted with 75 ml of water. It is then extracted with ethyl acetate and the obtained organic phase washed with 2N sodium carbonate solution. After evaporation of the ethyl acetate, the 5-methyl - 10,11 - dihydro[b,f]azepine - 3-acetic acid methyl ester remains as a colourless oil.

The 5 - butyl - 10,11 - dihydro - 5H - dibenz[b,f]azepine - 3 - acetic acid methyl ester (oil) is produced analogously, starting with 1.8 g of 5 - butyryl - 10,11 - dihydro-5H - dibenz[b,f]azepine - 3 - acetic acid methyl ester.

EXAMPLE 6

5 - methyl - 10,11 - dihydro - 5H - dibenz-[b,f]azepine - 3 - acetic acid.

A mixture of 24 g of 3-acetyl-5-methyl-10, 11-dihydro-5H-dibenz[b,f]azepine, 5 g of sulphur and 50 ml of morpholine is refluxed for 18 hours. After cooling, the reaction mixture is taken up in ethyl acetate and washed with 2N hydrochloric acid. The organic phase is concentrated by evaporation and the residue, which contains the 4 - (5 - methyl-10,11 - dihydro - 5H - dibenz[b,f]azepine-3 - thioacetyl) - morpholine, is refluxed with 15 g of potassium hydroxide in 250 ml of absolute ethylene glycol for 4 1/2 hours. The reaction mixture is poured on to 1200 ml of water and extracted with ether. The aqueous-alkaline phase is made acid with 5N hydro-

chloric acid and extracted with ether. After evaporation of the solvent, the residue is recrystallised from cyclohexane. The obtained 5 - methyl - 10,11 - dihydro - 5H - dibenz[b,f]azepine - 3 - acetic acid melts at 140—141°.

The starting material for the above example is produced as follows:

3 - acetyl - 5 - methyl - 10,11 - dihydro-5H - dibenz[b,f]azepine.

13 g of 3 - acetyl - 10,11 - dihydro - 5H-dibenz[b,f] azepine are heated with 60 ml of methanol and 28 ml of methyl iodide in a bomb tube for 24 hours at 100°. The brown solution is concentrated by evaporation. The residue is taken up in methylene chloride, decolorised with sodium thiosulphate, dried with sodium sulphate and concentrated by evaporation. The 3-acetyl-5-methyl-5H-dibenz[b,f]azepine remains behind as a yellowish oil, which does not crystallise and which can be directly further processed.

Example 7

10,11 - dihydro - 5H - dibenz[b,f]azepine-3 - acetic acid.

A mixture of 28.0 g of 3,5-diacetyl-10,11-dihydro-5H-dibenz[b,f]azepine, 5.0 g of sulphur and 50 ml of morpholine is refluxed for 18 hours. After cooling, the reaction mixture is taken up in ethyl acetate and washed with 2N hydrochloric acid. The organic phase is concentrated by evaporation and the residue, which contains the 4 - (5 - acetyl-10,11 - dihydro - 5H - dibenz[b,f] azepine-3 - thioacetyl) - morpholine, is refluxed with 35.0 g of potassium hydroxide in 350 ml of absolute ethylene glycol for 4 1/2 hours. The reaction mixture is poured on to 1200 ml of water and extracted with ether. The aqueous-alkaline solution is made acid with 5N hydrochloric acid and extracted with ether. After evaporation of the solvent, the residue is recrystallised from benzene. The 10,11 - dihydro - 5H - dibenz[b,f]azepine - 3 - acetic acid is contained as colourless crystals, which melt at 133—135°.

7 - chloro - 10,11 - dihydro - 5H - dibenz[b,f]azepine - 3 - acetic acid, M.P. 155—157° (from benzene) is obtained analogously, starting with 3,5 - diacetyl - 7 - chloro - 10,11 - dihydro - 5H - dibenz[b,f]azepine (oil).

The 3,5 - diacetyl - 7 - chloro - 10,11 - dihydro - 5H - dibenz[b,f]azepine starting material produced as follows:

a) 3 - chloro - 5 - acetyl - 10,11 - dihydro-5H - dibenz[b,f] azepine.

A solution of 300 g (1.31 mol) of 3-chloro - 10,11 - dihydro - 5H - dibenz[b,f]-azepine in 1000 ml of absolute benzene is mixed dropwise at 60—70° with a solution of 125 g (1.59 mol) of acetyl chloride in 600 ml of absolute benzene. The brown solution is refluxed for 5 hours and, after cooling, it is mixed with 200 ml of water and stirred for 1 hour at 20—25°. The upper organic phase is separated, washed with diluted ammonia and brine and dried over sodium sulphate. After evaporation of the benzene, the residue is recrystallised from ethanol. The 3 - chloro-5 - acetyl - 10,11 - dihydro - 5H - dibenz-[b,f]azepine melts at 119—120°.

b) 3,5 - diacetyl - 7 - chloro - 10,11 - dihydro - 5H - dibenz[b,f]azepine.

A suspension of 163.5 g (0.6 mol) of 3-chloro - 5 - acetyl - 10,11 - dihydro - 5H-dibenz[b,f]azepine in 850 ml of carbon disulphide is mixed at 40° with a few crystals of iodine and 135 g (1.72 mol) of acetyl chloride. 250 g (1.87 mol) of aluminium chloride are added within one hour and the mixture is then refluxed for one hour. A further 125 g (0.94 mol) of aluminium chloride are now added and the brown suspension is refluxed for 12 hours. After addition, each time, of 66.6 g (0.5 mol) of aluminium chloride and 26.1 g (0.33 mol) of acetyl chloride, the suspension is boiled in each case for a further 24 hours. This process is repeated six times, so that the reaction mixture can be prepared after one week. The carbon disulphide is decanted and the brown resin remaining behind is triturated with diluted hydrochloric acid and ice, and subsequently extracted with ethyl acetate. The organic phase is washed with 2N sodium carbonate solution and brine, dried over sodium sulphate and concentrated by evaporation. The oily residue can be further used without purification. Analytically pure 3,5 - diacetyl - 7 - chloro - 10,11 - dihydro - 5H - dibenz[b,f]azepine is obtained by chromatography on 40 times the amount of silica gel. It is eluted with benzene/ether 1:1 and exists as oil.

Example 8

5 - methyl - 10,11 - dihydro - 5H - dibenz-[b,f]azepine - 3 - acetic acid.

A solution of 10.0 g of 5 - methyl - 10,11-dihydro - 5H - dibenz[b,f]azepine - 3-acetonitrile in 500 ml of chloroform and 50 ml of abs. ethanol is saturated at 0—5° with hydrogen chloride and the solution, after stirring for 14 hours, is concentrated by evaporation at 20—25°. The oily imido ester hydrochloride is refluxed for one hour with 100 ml of ethanol and 30 ml of 5N sodium hydroxide solution. The ethanol is distilled off and the alkaline solution remaining behind is acidified with 2N hydrochloric acid. The formed aqueous suspension is extracted with ethyl acetate and the organic phase then repeatedly extracted with 2N sodium carbonate solution. The sodium carbonate solutions are combined and acidified with 2N hydrochloric acid. The precipitated, pale yellow crystals are filtered by suction and recrystallised from cyclohexane. The 5 - methyl - 10,11 - di-

hydro - 5H - dibenz[b,f]azepine - 3 - acetic acid, M.P. 140—141° is obtained.

EXAMPLE 9

5 - methyl - 10,11 - dihydro - 5H - dibenz[b,f]azepine - 2 - acetic acid.

A mixture consisting of 5.2 g of 2 - acetyl-5 - methyl - 10,11 - dihydro - 5H - dibenz[b,f]azepine, 2.1 g of sulphur and 6.1 g of morpholine is refluxed for 15 hours (bath temperature 150°). After cooling, the reaction mixture is taken up in benzene. The benzene solution is filtered through a layer of neutral aluminium oxide and the filtrate is concentrated by evaporation to dryness under 11 Torr. The 4 - (5 - methyl - 10,11 - dihydro - 5H - dibenz[b,f]azepine - 2 - thioacetyl) - morpholine remaining behind is refluxed with 6 g of potassium hydroxide in 100 ml of abs. ethylene glycol for 4 1/2 hours. The reaction mixture is poured on to 900 ml of water and extracted with ether. The aqueous-alkaline phase is made acid with concentrated hydrochloric acid and extracted with ether. The ether phase is washed with water, dried over magnesium sulphate and concentrated by evaporation to dryness under 11 Torr. The 5 - methyl - 10,11 - dihydro-5H - dibenz[b,f]azepine - 2 - acetic acid crystallises from ether/petroleum ether, M.P. 121—123°.

The starting materials for the above example are produced as follows:

a) 5 - methyl - 10,11 - dihydro - 5H - dibenz[b,f]azepine - 2 - carboxaldoxime.

A solution of 23.7 g of 5 - methyl - 10,11-dihydro - 5H - dibenz[b,f]azepine - 2-carboxaldehyde (M.P. 90—93°), 17.5 g of hydroxylamine-hydrochloride and 18 ml of pyridine in 200 ml of ethanol is refluxed for one hour. The solution is cooled and concentrated to dryness under 11 Torr at 50°. The residue is mixed with 150 ml of water and extracted with ether. The ethereal solution is extracted with water, dried over magnesium sulphate and concentrated under 11 Torr, whereby the 5 - methyl - 10,11 - dihydro - 5H - dibenz[b,f]azepine - 2 - carboxaldoxime crystallises out. Recrystallised from ether/petroleum ether, the substance melts at 148—150°.

b) 2 - cyano - 5 - methyl - 10,11 - dihydro-5H - dibenz[b,f]azepine.

A solution of 30.3 g of 5 - methyl - 10,11-dihydro - 5H - dibenz[b,f]azepine - 2-carboxaldoxime in 180 ml of acetic anhydride is refluxed for 2 hours. The solution is then cooled and concentrated to dryness under 11 Torr at 40°. The residue is dissolved in ethanol, the ethanolic solution boiled up with active charcoal and filtered. The filtrate is somewhat concentrated under 11 Torr and is left to stand at room temperature, whereby the 2 - cyano - 5 - methyl - 10,11 - dihydro-5H - dibenz[b,f]azepine slowly crystallises out, M.P. 120—122°.

c) 2 - acetyl - 5 - methyl - 10,11 - dihydro-5H - dibenz[b,f] azepine.

70 ml of absolute benzene are added to a Grignard solution consisting of 6 g of magnesium and 3.5 g of methyl iodide in 200 ml of ether. The Grignard solution is then mixed with a solution of 23.4 g of 2 - cyano - 5-methyl - 10,11 - dihydro - 5H - dibenz[b,f]-azepine in 150 ml of ether. The mixture is then refluxed for 5 hours, cooled and 300 ml of water and 300 ml of ether are then added, whereupon the mixture is refluxed for 10 hours. The ether solution is then separated, washed with water, dried over magnesium sulphate and concentrated to dryness under 11 Torr. The residue is dissolved in ether. The ether solution is filtered through a layer of neutral aluminium oxide and concentrated under 11 Torr. The 2 - acetyl - 5-methyl - 10,11 - dihydro - 5H - dibenz[b,f]-azepine crystallises from ether/petroleum ether, M.P. 80—83°.

EXAMPLE 10

5 - methyl - 10,11 - dihydro - 5H - dibenz[b,f]azepine - 2 - acetic acid.

2 g of 5 - methyl - 10,11 - dihydro - 5H-dibenz[b,f]azepine - 2 - acetamide are refluxed with 9 g of potassium hydroxide in 60 ml of n-butanol for one hour. The solution is then concentrated under 0.1 Torr at 60°, and the residue is dissolved in water. The aqueous solution is extracted with ether, separated and acidified with concentrated hydrochloric acid. The precipitated oil is extracted with ether. The ether solution is washed with water, dried over magnesium sulphate and concentrated to dryness under 11 Torr. The residue is crystallised from ether/petroleum ether. The 5 - methyl - 10, 11 - dihydro - 5H - dibenz[b,f]azepine - 2-acetic acid melts at 121—123°.

The starting material for the above example is produced as follows:

5 - methyl - 10,11 - dihydro - 5H - dibenz[b,f]azepine - 2 - acetamide.

A solution of 5 g of 5 - methyl - 10,11-dihydro - 5H - dibenz[b,f]azepine - 2-acetonitrile (M.P. 70—71°) in 50 ml of acetone and 10 ml of water is mixed at 20° with 6 ml of 30% aqueous hydrogen peroxide solution and subsequently with 2 ml of 2N sodium hydroxide solution. The reaction solution is heated for 20 minutes at 50°, whereby evolution of oxygen occurs. A further 6 ml of 30% hydrogen peroxide solution and 2 ml of 2N sodium hydroxide solution are added and the mixture is heated for a further 4 hours at 50°. The reaction solution is then concentrated to dryness under 11 Torr at 50°. The residue is dissolved in methanol. The methanolic solution is boiled up with active charcoal and filtered. The filtrate is

concentrated somewhat under 11 Torr, whereby the 5 - methyl - 10,11 - dihydro - 5H-dibenz[b,f]azepine - 2 - acetamide crystallises out, M.P. 140—142°.

EXAMPLE 11

5 - methyl - 10,11 - dihydro - 5H - dibenz-[b,f]azepine - 2 - acetic acid.

To a solution of 75 g of potassium hydroxide in 500 ml of n-butanol are added 16 g of 5 - methyl - 10,11 - dihydro - 5H-dibenz[b,f]azepine - 2 - acetonitrile. The mixture is refluxed for 2 hours, cooled and concentrated by evaporation to dryness under 0.01 Torr at 60°. The residue is dissolved in 1500 ml of water. The aqueous solution is extracted three times with 300 ml of ether each time, separated and acidified at 5° with 2N hydrochloric acid. The precipitated oil is extracted with ether. The ether solution is separated, washed with water, dried with magnesium sulphate and concentrated by evaporation to dryness under 11 Torr. The residue is crystallised from ether/petroleum ether. The 5 - methyl - 10,11 - dihydro - 5H - dibenz[b,f]azepine - 2 - acetic acid melts at 121—123°.

The following is produced analogously:

7 - chloro - 5 - methyl - 10,11 - dihydro-5H - dibenz[b,f] azepine - 2 - acetic acid, M.P. 175—187° (from ethyl acetate/petroleum ether) is obtained, starting with 10 g of 7 - chloro - 5 - methyl - 10,11 - dihydro - 5H - dibenz[b,f]azepine - 2 - acetonitrile, M.P. 117—119°.

EXAMPLE 12

5 - methyl - 10,11 - dihydro - 5H - dibenz-[b,f]azepine - 3 - acetic acid.

A mixture of 13 g of 5 - methyl - 10,11-dihydro - 5H - dibenz[b,f]azepine - 3-acetonitrile, 15 g of potassium hydroxide and 250 ml of absolute ethylene glycol is refluxed for 4 1/2 hours. The reaction mixture is poured on to 1200 ml of water and extracted with ether. The aqueous-alkaline phase is made acid with 5N hydrochloric acid and extracted with ether. After evaporation of the solvent, the residue is recrystallised from cyclohexane. The obtained 5 - methyl-10,11 - dihydro - 5H - dibenz[b,f]azepine-3 - acetic acid melts at 140—141°.

EXAMPLE 13

2 - (5 - methyl - 10,11 - dihydro - 5H - dibenz[b,f]azepine - 2) - butyric acid.

A solution of 14.8 g of 5 - methyl - 10,11-dihydro - 5H - dibenz[b,f]azepine - 2 - acetic acid ethyl ester in 50 ml of hexamethyl phosphoric acid triamide is added at 40° under nitrogen to a suspension of 2.5 g of sodium hydride/mineral oil (1:1) in 80 ml of hexamethyl phosphoric acid triamide. The mixture is stirred for 45 minutes at 50° and cooled to 30°, whereupon 7.8 g of ethyl iodide are added dropwise. The mixture is then stirred for 10 hours at 60°, cooled and is poured on to 1000 ml of ice water. The mixture is extracted four times with 300 ml of ether each time. The ether extracts are washed with water, dried over sodium sulphate and concentrated by evaporation under 11 Torr. The residue which, as starting material for the actual saponification, contains the 2 - (5 - methyl - 10,11 - dihydro - 5H - dibenz[b,f]azepine - 2) - butyric acid ethyl ester, is dissolved in 300 ml of ethanol and 100 ml of 2N sodium hydroxide solution. The solution is refluxed for 3 hours and concetnrated to dryness under 11 Torr. The residue is dissolved in 500 ml of water, the aqueous solution is extracted with 100 ml of ether, separated and acidified with 2N hydrochloric acid. The precipitated oil is extracted with ethyl acetate. The ethyl acetate solution is washed with water, dried over magnesium sulphate and is concentrated to dryness under 11 Torr. The residue, an oil, is chromatographed on 30 g of silica gel. The fractions, 4—6, eluted with benzene/ethyl acetate (2:1), are combined and concentrated by evaporation to dryness under 11 Torr. The residue is crystallised from ether/petroleum ether. The 2 - (5 - methyl - 10,11 - dihydro - 5H - dibenz[b,f]azepine - 2)-butyric acid melts at 108—113°.

The starting material for the above given example is produced as follows:

5 - methyl - 10,11 - dihydro - 5H - dibenz[b,f]azepine - 2 - acetic acid ethyl ester.

A solution consisting of 32 g of 5 - methyl-10,11 - dihydro - 5H - dibenz[b,f]azepine-2 - acetic acid in 120 ml of 1N sodium hydroxide solution is concentrated by evaporation to dryness under 11 Torr at 50°. The residue is mixed with 100 ml of absolute benzene and the solution is again concentrated by evaporation to dryness under 11 Torr at 50°. The residue is dissolved in 350 ml of absolute dimethyl formamide. The solution is mixed at 40° with 18.5 g of diethyl sulphate. After 15 minutes, a further 5 g of diethyl sulphate are added, the mixture is stirred for 30 minutes at 40° and is poured on to ice water. The precipitated oil is extracted with ether. The ether solution is extracted with 1N sodium carbonate solution and then with water, is separated, dried over magnesium sulphate and concentrated under 11 Torr at 40°. The residue is distilled in high vacuum. The 5 - methyl - 10,11 - dihydro - 5H - dibenz[b,f]azepine - 2-acetic acid ethyl ester boils at 170°/0.001 Torr.

EXAMPLE 14

10,11 - dihydro - 5H - dibenz[b,f]azepine-3 - acetic acid.

8.8 g of 5 - acetyl - 10,11 - dihydro - 5H-dibenz[b,f] azepine - 3 - acetic acid are re-

fluxed with 8 g of potassium hydroxide in 120 ml of ethylene glycol for 8 hours under nitrogen. After cooling, the mixture is mixed with water, acidified with 2N hydrochloric acid and extracted with ethyl acetate. The organic phase is concentrated by evaporation and the crystals remaining behind are recrystallised from benzene, whereby the 10,11-dihydro - 5H - dibenz[b,f] azepine - 3-acetic acid, M.P. 133—135°, is obtained.

The 10,11 - dihydro - 5H - dibenz[b,f]-azepine - 3 - acetic acid, M.P. 133—135°, is obtained analogously, starting with 5-butyryl - 10,11 - dihydro - 5H - dibenz[b,f]-azepine - 3 - acetic acid (colourless oil).

The 7 - chloro - 10,11 - dihydro - 5H-dibenz[b,f] azepine - 3 - acetic acid, M.P. 155—157° (from benzene), is obtained analogously, starting with 4.5 g of 7 - chloro-5 - acetyl - 10,11 - dihydro - 5H - dibenz-[b,f] azepine - 3 - acetic acid, M.P. 128—129°.

α - methyl - 10,11 - dihydro - 5H - dibenz[b,f]azepine - 3 - acetic acid, M.P. 129—135°, is obtained analogously, starting with 2.0 g of α - methyl - 5 - acetyl - 10,11-dihydro - 5H - dibenz[b,f]azepine - 3 - acetic acid, M.P. 153—154°.

The starting materials for the above process can be produced as follows:

a) 5 - acetyl - 10,11 - dihydro - 5H - dibenz[b,f]azepine - 3 - carboxylic acid.

83.5 g of 3,5-diacetyl-10,11-dihydro-5H-dibenz[b,f]azepine (cf. Helv. Chim. Acta 44, 753—762, especially 761 (1961)) are dissolved in 750 ml of dioxane and, while stirring, 375 ml of 17.8% aqueous sodium hypochlorite solution are added dropwise at 0° within 30 minutes. The reaction mixture is stirred firstly for 30 minutes at 0° and then for 2 hours at room temperature, whereupon the dioxane is evaporated off under vacuum. The aqueous phase remaining behind is washed with ether and then acidified with concentrated hydrochloric acid. The precipitated resin is taken up in sodium hydrogen carbonate solution, the solution is filtered and acidified with dilute hydrochloric acid. The precipitated crystals are filtered under suction, dried and recrystallised from acetone. The thus obtained 5 - acetyl - 10,11-dihydro - 5H - dibenz[b,f] azepine - 3-carboxylic acid melts at 197—198°.

The following is obtained analogously:

5 - acetyl - 7 - chloro - 10,11 - dihydro-5H - dibenz[b,f] azepine - 3 - carboxylic acid, M.P. 264—266° (from ether/petroleum ether) is obtained, starting with 62.7 g of 3,5 - diacetyl - 7 - chloro - 10,11 - dihydro-5H - dibenz[b,f]azepine.

b) 5 - acetyl - α - methyl - 10,11 - dihydro-5H - dibenz[b,f] azepine - 3 - methanol.

A suspension of 56.0 g of 3,5 - diacetyl-10,11 - dihydro - 5H - dibenz[b,f]azepine in 300 ml of absolute methanol is mixed with 10 g of sodium boron hydride at 5—10° within one hour. The mixture is mixed for 2 hours in the ice bath and for 2 hours at 20—25°, is poured on to ice cold 2N hydrochloric acid and extracted with ethyl acetate. The 5 - acetyl - α - methyl - 10,11 - dihydro-5H - dibenz[b,f]azepine - 3 - methanol is obtained as colourless oil.

The 5 - formyl - α - methyl - 10,11 - dihydro - 5H - dibenz[b,f]azepine - 3-methanol (3 - (1 - hydroxyethyl) - 10,11-dihydro - 5H - dibenz[b,f]azepine - 5-carboxaldehyde) is analogously obtained as hygroscopic crystals, M.P. 111—113°, starting from 3-acetyl-5-formyl-10,11-dihydro-5H-dibenz[b,f]azepine.

3 - (1 - bromethyl) - 5 - acetyl - 10,11-dihydro - 5H - dibenz[b,f] azepine.

15 g of the above reduction product are dissolved in 150 ml of chloroform and mixed, while cooling with ice, with 35 ml of phosphorus tribromide in 50 ml of chloroform within 40 minutes at 0—5°. The mixture is stirred for 8 hours at 20—25° and then poured on to ice water. The 3 - (1 - bromethyl) - 5 - acetyl - 10,11 - dihydro - 5H-dibenz[b,f]azepine is obtained as colourless oil after extraction of the mixture with chloroform and washing of the organic phase with 2N sodium hydrogen carbonate solution.

5 - acetyl - α - methyl - 10,11 - dihydro-5H - dibenz[b,f] azepine - 3 - acetonitrile.

10 g of the above bromine compound are stirred under nitrogen with 5 g of potassium cyanide in 100 ml of dimethyl sulphoxide for 4 hours at 40—50°. The reaction mixture is then poured on to water and extracted with ether. The organic phase is concentrated by evaporation, whereby the 5 - acetyl - α-methyl - 10,11 - dihydro - 5H dibenz[b,f]-azepine - 3 - acetonitrile remains behind as a colourless oil and, in a known manner, it is then hydrolysed to give 5 - acetyl - α-methyl - 10,11 - dihydro - 5H - dibenz[b,f]-azepine - 3 - acetic acid.

c) 5 - acetyl - 10,11 - dihydro - 5H - dibenze[b,f]azepine - 3 - carboxylic acid methyl ester.

162.0 g of 5 - acetyl - 10,11 - dihydro-5H - dibenz[b,f] azepine - 3 - carboxylic acid are refluxed with 6.0 g of *p*-toluene sulphonic acid in 1500 ml of methanol for 14 hours. After evaporating off the methanol, the residue is taken up in ethyl acetate and is extracted three times with 2N sodium carbonate solution. The organic phase is concentrated by evaporation and the 5 - acetyl-10,11 - dihydro - 5H - dibenz[b,f]azepine-3 - carboxylic acid methyl ester, M.P. 122—124°, is thus obtained.

5 - acetyl - 7 - chloro - 10,11 - dihydro-5H - dibenz[b,f] azepine - 3 - carboxylic acid methyl ester, M.P. 130—132° (from methanol) is obtained, starting with 18.5 g of

5 - acetyl - 7 - chloro - 10,11 - dihydro-5H - dibenz[b,f]azepine - 3 - carboxylic acid, M.P. 264—266°.

d) 5 - acetyl - 10,11 - dihydro - 5H - dibenz[b,f]azepine - 3 - methanol.

40 g of the above methyl ester in 400 ml of freshly distilled absolute tetrahydrofuran are mixed in portions, with a suspension of 10.4 g of lithium aluminium hydride in 100 ml of absolute tetrahydrofuran at −70° within 30 minutes. The mixture is stirred for 2 hours at −70° and then mixed at −50 to −70° with 10 ml of ethyl acetate and, following this, with 50 ml of saturated ammonium chloride solution. The mixture is heated at 10—20° and extracted with ethyl acetate. The organic phase is washed with 2N sodium carbonate solution, dried and concentrated by evaporation. The residue of crude 5-acetyl - 10,11 - dihydro - 5H - dibenz[b,f]-azepine - 3 - methanol is recrystallised from benzene, M.P. 118—120°.

5 - acetyl - 7 - chloro - 10,11 - dihydro-5H - dibenz[b,f] azepine - 3 - methanol is obtained, starting with 11.4 g of 5 - acetyl-7 - chloro - 10,11 - dihydro - 5H - dibenz-[b,f] azepine - 3 - carboxylic acid methyl ester, M.P. 130—132°.

e) 3 - bromomethyl - 5 - acetyl - 10,11-dihydro - 5H - dibenz[b,f]azepine.

30 g of the above reduction product are dissolved in 300 ml of chloroform and mixed, while cooling with ice, at 0—5° with 70 ml of phosphorus tribromide in 100 ml of chloroform within 40 minutes. The mixture is stirred for 8 hours at 20—25° and is then poured on to ice water. The 3 - bromomethyl - 5 - acetyl - 10,11 - dihydro - 5H-dibenz[b,f]azepine is obtained as white crystals, M.P. 106—107° (from ether) after extraction of the mixture with chloroform and washing of the organic phase with 2N sodium hydrogen carbonate solution.

f) 5 - acetyl - 10,11 - dihydro - 5H - dibenz[b,f]azepine 3 - acetonitrile.

20 g of the above bromine compound are stirred under nitrogen with 10 g of potassium cyanide in 200 ml of dimethyl sulphoxide for 4 hours at 40—50°. The reaction mixture is then poured on to water and extracted with ether. The organic phase is concentrated by evaporation, whereby the 5-acetyl - 10,11 - dihydro - 5H - dibenz[b,f]-azepine - 3 - acetonitrile remains behind as white crystals, M.P. 97—100° (from benzene/petroleum ether).

5 - acetyl - 7 - chloro - 10,11 - dihydro-5H - dibenz[b,f] azepine - 3 - acetonitrile, M.P. 112—114° (from benzene/petroleum ether) is obtained, starting with 8 g of 3-bromomethyl - 5 - acetyl - 7 - chloro - 10,11-dihydro[b,f] azepine.

g) 5 - acetyl - 10,11 - dihydro - 5H - dibenz[b,f]azepine - 3 - acetic acid.

13.8 g of 5 - acetyl - 10,11 - dihydro - 5H-dibenz[b,f] azepine - 3 - acetonitrile are dissolved in 60 ml of absolute ethanol and 300 ml of chloroform. The solution is saturated at 0—10° with hydrogen chloride and is stirred for 8 hours at 20—25°. After evaporating off the solvent, the residue is taken up in 120 ml of dioxane and 20 ml of water and is stirred for 3 hours at 40°. The solution is then concentrated by evaporation and the residue divided between ethyl acetate and 2N sodium hydrogen carbonate solution. The organic phase is dried and concentrated by evaporation. The obtained oily ethyl ester is stirred with 100 ml of ethanol and 30 ml of 2N sodium hydroxide solution for 16 hours at 20—25°. After evaporating off the ethanol, the basic suspension is washed twice with ether and is made acid with 2N hydrochloric acid. The pale crystals are filtered by suction and recrystallised from ethyl acetate/petroleum ether, whereby the 5 - acetyl - 10,11 - dihydro - 5H - dibenz-[b,f]azepine - 3 - acetic acid, M.P. 163—165°, is obtained.

5 - acetyl - 7 - chloro - 10,11 - dihydro-5H - dibenz[b,f] azepine - 3 - acetic acid, M.P. 128—129° (from benzene) is obtained analogously, starting with 6.9 g of 5 - acetyl-7 - chloro - 10,11 - dihydro - 5H - dibenz-[b,f] azepine - 3 - acetonitrile, M.P. 112—114°.

Example 15

10,11 - dihydro - 5H - dibenz[b,f]azepine-2 - acetic acid.

1.37 g of 5 - benzyl - 10,11 - dihydro-5H - dibenz[b,f] azepine - 2 - acetic acid are dissolved in 40 ml of absolute methanol and, after addition of 0.25 g of palladium charcoal (catalyst 10% Pd), hydrogenated at room temperature and under normal pressure. The hydrogenation is finished after 15 minutes. The mixture is filtered and the filtrate concentrated by evaporation under 11 Torr at 40°. The residue is crystallised from ether/petroleum ether. The 10,11 - dihydro-5H - dibenz[b,f]azepine - 2 - acetic acid melts at 155—158°.

The starting material for the above example is produced as follows:

5 - benzyl - 10,11 - dihydro - 5H - dibenz[b,f]azepine - 2 - acetic acid.

4 g of 5 - benzyl - 10,11 - dihydro - 5H-dibenz[b,f] azepine - 2 - acetonitrile, M.P. 96—98°, are refluxed with 6 g of potassium hydroxide in 40 ml of butanol for 7 hours. The solution is cooled and then concentrated under 0.1 Torr at 60—70°, whereby the residue is dissolved in water. The aqueous-alkaline solution is extracted with ether, separated and acidified with 2N hydrochloric acid. The precipitated oil is extracted with ether. The ethereal solution is washed with water, dried over magnesium sulphate and concentrated by evaporation. The residue, a

yellow oil, crystallises from ether. The 5-benzyl - 10,11 - dihydro - 5H - dibenz[b,f]-azepine - 2 - acetic acid melts at 138—139°.

EXAMPLE 16

5 - methyl - 10,11 - dihydro - 5H - dibenz-[b,f]azepine - 3 - acetic acid.

7.0 g of 10,11-dihydro-5H-dibenz[b,f]-azepin - 3 - acetic acid are heated with 14 ml of methyl iodide and 70 ml of chloroform in a closed tube at 100° for 24 hours. The brown reaction solution is decolourised with sodium thiosulphate solution and concentrated by evaporation. After recrystallising from cyclohexane, the obtained 5 - methyl-10,11 - dihydro - 5H - dibenz[b,f]azepine-3 - acetic acid melts at 140—141°.

EXAMPLE 17

5 - methyl - 10,11 - dihydro - 5H - dibenz-[b,f]azepine - 3 - acetic acid.

14.0 g of 10,11 - dihydro - 5H - dibenz-[b,f]azepine - 3 - acetic acid are heated with 70 ml of methanol and 28 ml of methyl iodide in a closed tube at 100° for 24 hours. The brown solution is concentrated by evaporation and the residue is dissolved in methylene chloride. The solution is decolourised with sodium thiosulphate solution and then extracted with 2N sodium carbonate solution. The aqueous alkaline phase is acidified with 2N hydrochloric acid and the 5-methyl - 10,11 - dihydro - 5H - dibenz-[b,f]azepine - 3 - acetic acid precipitates. The organic phase is concentrated by evaporation and the 5 - methyl - 10,11 - dihydro - 5H - dibenz[b,f]azepine - 3 - acetic acid methyl ester, which is obtained as residue, is boiled with 200 ml of ethanol and 40 ml of 2N sodium hydroxide solution for 15 minutes. After concentrating the solution by evaporation and acidifying the residue, the principal amount of 5 - methyl - 10,11 - dihydro - 5H - dibenz[b,f]azepine - 3 - acetic acid is obtained, M.P. 140—141°, after recrystallisation from cyclohexane.

EXAMPLE 18

7 - chloro - 5 - methyl - 10,11 - dihydro-5H - dibenz[b,f]azepine - 3 - acetic acid.

16.0 g of 7 - chloro - 10.11 - dihydro-5H - dibenz[b,f] azepine - 3 - acetic acid are heated with 70 ml of methanol and 28 ml of methyl iodide at 100° in a closed tube for 24 hours. The brown solution is concentrated by evaporation and the residue is dissolved in methylene chloride. The solution is decolourised with sodium thiosulphate solution and then extracted with 2N sodium carbonate solution. The aqueous, alkaline phase is acidified with 2N hydrochloric acid, whereby 7 - chloro - 5 - methyl - 10,11-dihydro - 5H - dibenz[b,f]azepine - 3-acetic acid precipitates. The organic phase is concentrated by evaporation and the 7-chloro - 5 - methyl - 10,11 - dihydro - 5H-dibenz[b,f]azepine - 3 - acetic acid methyl ester obtained as residue is cleared of impurities by being added to a mixture of 80 ml of acetic anhydride and 40 ml of formic acid, which has been previously stirred for one hour at 40°, and stirred for 8 hours at 20—25°. Two hours after the addition of 100 ml of water, the mixture is extracted with ethyl acetate, washed with 2N sodium carbonate solution and concentrated by evaporation. The residue is chromatographed on 30 times the amount of silica gel. The 7 - chloro-5 - methyl - 10,11 - dihydro - 5H - dibenz-[b,f]azepine - 3 - acetic acid methyl ester is eluted with benzene and boiled with 200 ml of ethanol and 40 ml of 2N sodium hydroxide solution for 15 minutes. After concentrating the solution by evaporation and acidifying the residue, the principal amount of 7 - chloro - 5 - methyl - 10,11 - dihydro-5H - dibenz[b,f]azepine - 3 - acetic acid is obtained, M.P. 156—158° (from ether/petroleum ether).

EXAMPLE 19

2 - (5 - methyl - 10,11 - dihydro - 5H - dibenz[b,f]azepine - 2) - propionic acid.

A mixture of 5.5 g of methyl - (5-methyl - 10,11 - dihydro - 5H - dibenz[b,f]-azepine - 2) - malonic acid diethyl ester, 3.5 g of potassium hydroxide, 12 ml of water and 40 ml of n-butanol is refluxed for 4 hours to boiling. The mixture is then concentrated to dryness under 11 Torr and the residue is dissolved in 500 ml of water. The aqueous solution is extracted with ether, separated and acidified with 2N hydrochloric acid. The precipitated oil is extracted with ether. The ether solution is washed with water, dried over magnesium sulphate and concentrated by evaporation under 11 Torr. The residue is crystallised twice from ethyl acetate, whereby the 2 - (5 - methyl - 10,11-dihydro - 5H - dibenz[b,f] azepine - 2)-propionic acid M.P. 153—157° is obtained.

2 - (5 - methyl - 10,11 - dihydro - 5H-dibenz[b,f]azepine - 2) - butyric acid, M.P. 108—113° (from ether/petroleum ether) is obtained analogously, starting with 10 g of ethyl - (5 - methyl - 10,11 - dihydro - 5H-dibenz[b,f] azepine - 2) - malonic acid diethyl ester (oil).

The starting materials are produced as follows:

a) 5 - methyl - 10,11 - dihydro - 5H - dibenz[b,f]azepine - 2 - malonic acid diethyl ester.

A mixture of 11.8 g of 5 - methyl - 10,11-dihydro - 5H - dibenz[b,f]azepin - 2 - acetic acid ethyl ester (see example 13) and 37 ml of diethyl carbonate is heated at 80°. A solution of 1.32 g of sodium in 60 ml of absolute ethanol is added dropwise at 80°. The ethanol is then distilled off from the

reaction mixture. The bath temperature is then slowly increased to 220° and a further 30 ml of diethyl carbonate are added. 20 ml of diethyl carbonate are distilled off during ca. 1/2 hour. The contents of the flask are cooled and neutralised with a mixture of 6.4 ml of glacial acetic acid and 110 ml of ice water. The mixture is extracted twice, each time with 100 ml of ether, and the ether solution is washed with 1N potassium bicarbonate solution and water, dried over sodium sulphate and concentrated under 11 Torr. The residue, a yellow oil, is distilled in high vacuum. The 5 - methyl - 10,11-dihydro - 5H - dibenz[b,f]azepine - 2-malonic acid diethyl ester boils at 190—195°/0.001 Torr.

b) Methyl - (5 - methyl - 10,11 - dihydro-5H - dibenz [b,f]azepine - 2) - malonic acid diethyl ester.

0.5 g of sodium are dissolved in 80 ml of absolute ethanol. The solution is heated at 50° and is mixed with a solution of 5.9 g of 5 - methyl - 10,11 - dihydro - 5H - dibenz[b,f]azepine - 2 - malonic acid diethyl ester in 15 ml of absolute ethanol. The mixture is stirred for 1/2 hour at 50° and then 3.5 g of methyl iodide are quickly added dropwise. The reaction mixture is then refluxed, while stirring, for 4 hours and is again mixed with 3.5 g of methyl iodide. After refluxing for a further 2 hours, the reaction mixture is concentrated by evaporation under 11 Torr. The residue is dissolved in 70 ml of ether. The ether solution is washed with, in each case, 10 ml of 10% sodium bisulphite solution and water, is dried over sodium sulphate and concentrated by evaporation under 11 Torr. The methyl - (5-methyl - 10,11 - dihydro - 5H - dibenz[b,f]-azepine - 2) - malonic acid diethyl ester is obtained as yellow oil.

Ethyl - (5 - methyl - 10,11 - dihydro - 5H-dibenz[b,f] azepine - 2) - malonic acid diethyl ester (oil) is obtained analogously, starting with 6.3 g of 5 - methyl - 10,11 - dihydro - 5H - dibenz[b,f]azepine - 2 - malonic acid diethyl ester and ethyl iodide.

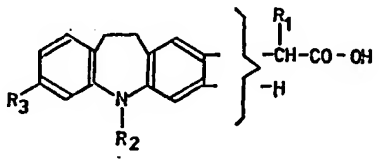
EXAMPLE 20

5 - methyl - 10,11 - dihydro - 5H - dibenz-[b,f]azepine - 2 - acetic acid sodium salt.

A solution of 13.4 g of 5 - methyl - 10,11-dihydro - 5H - dibenz[b,f]azepine - 2 - acetic acid in 50 ml of 1N sodium hydroxide solution is concentrated by evaporation to dryness at 50° under 11 Torr. The residue, a yellow oil, is crystallised from ethyl acetate. The 5 - methyl - 10,11 - dihydro - 5H-dibenz[b,f]azepine - 2 - acetic acid sodium salt melts at 192—194°.

WHAT WE CLAIM IS:—

1. A compound of the formula I



(I)

wherein

R_1 represents hydrogen or a lower alkyl group with at most 3 carbon atoms,

R_2 represents hydrogen or a lower alkyl group with at most 4 carbon atoms,

R_3 represents hydrogen or chlorine, or a pharmaceutically acceptable salt thereof with an organic or inorganic base.

2. 5 - Methyl - 10,11 - dihydro - 5H-dibenz[b,f]azepine - 3 - acetic acid or a pharmaceutically acceptable salt thereof with an organic or inorganic base.

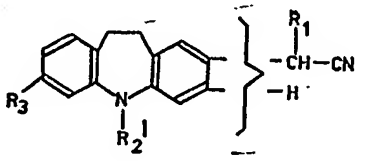
3. 10,11 - Dihydro - 5H - dibenz[b,f]-azepine - 2 - acetic acid or a pharmaceutically acceptable salt thereof with an organic or inorganic base.

4. 5 - Methyl - 10,11 - dihydro - 5H-dibenz[b,f]azepine - 2 - acetic acid or a pharmaceutically acceptable acid addition salt thereof with an organic or inorganic base.

5. α,5 - Dimethyl - 10,11 - dihydro - 5H-dibenz[b,f]azepine - 2 - acetic acid or a pharmaceutically acceptable addition salt thereof with an organic or inorganic base.

6. 5 - Methyl - 7 - chloro - 10,11 - dihydro - 5H - dibenz[b,f]azepine - 2 - acetic acid or a pharmaceutically acceptable salt thereof with an organic or inorganic base.

7. Process for the production of compounds having the formula I as defined in claim 1 and their pharmaceutically acceptable salts with bases, which comprises subjecting a compound having the formula II



(II)

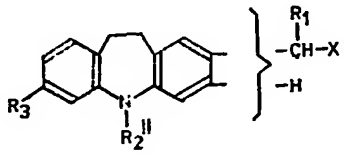
wherein R_1 and R_3 have the meaning given in claim 1 and

R_2' represents hydrogen, a lower alkyl group having at most 4 carbon atoms, a lower alkanoyl group having at most 4 carbon atoms or a benzyl group,

to alcoholysis with a lower alkanol having at most 6 carbon atoms, hydrolysing an obtained lower alkyl ester in an acid or alkaline medium and, when required, liberating the free carboxylic acid from a salt thereof with

a base thus produced, and/or converting a free carboxylic acid or a salt thereof with a base thus obtained into, or into another, pharmaceutically acceptable salt thereof with a base.

8. Process for the production of compounds having the formula I as defined in claim 1 and their pharmaceutically acceptable salts with bases, which comprises hydrolysing, in an acid or alkaline medium, a compound having the formula III



(III)

wherein R_1 and R_3 have the meanings given in claim 1,

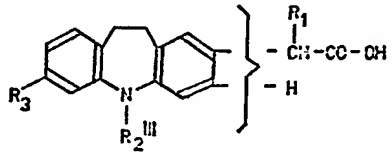
R_2'' represents hydrogen, a lower alkyl group having at most 4 carbon atoms, or a lower alkanoyl group having at most 4 carbon atoms, and

X represents a group which can be hydrolysed to a carboxyl group

and, when required, liberating the free carboxylic acid from a salt thereof with a base thus produced, and/or converting a free carboxylic acid or a salt thereof with a base thus obtained into, or into another, pharmaceutically acceptable salt thereof with a base.

9. Process as claimed in claim 8 wherein X represents a cyano, carboxylic acid imido ester, carboxylic acid ester or carbamoyl group or a thiocarbamoyl group optionally mono- or di-alkyl substituted at the nitrogen atom, whereby in the case of di-substitution, the alkyl groups may be bound by way of an oxygen atom.

10. Process for the production of compounds having the formula I as defined in claim 1, but wherein R_2 may represent a hydrogen atom only and their pharmaceutically acceptable salts with bases which comprises hydrolysing a compound having the formula V



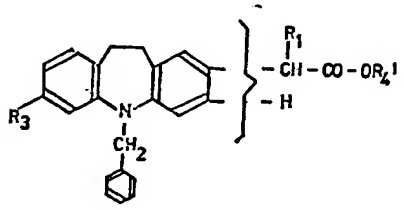
(V)

wherein R_2''' represents an alkanoyl group having at most 4 carbon atoms, and

R_1 and R_3 have the meanings given in claim 1

and, when required, liberating the free carboxylic acid from a salt thereof with a base thus produced, and/or converting a free carboxylic acid or a salt thereof with a base thus obtained into, or into another, pharmaceutically acceptable salt thereof with a base.

11. Process for the production of compounds having the formula I as defined in claim 1, but wherein R_2 may represent a hydrogen atom only and their pharmaceutically acceptable salts with bases which comprises reacting a compound having the formula VI



(VI)

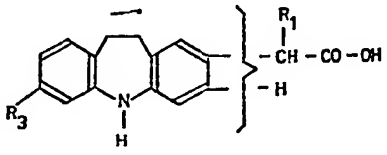
wherein R_1 and R_3 have the meanings given in claim 1 and

R_4' represents hydrogen, a lower alkyl group having at most 6 carbon atoms or a benzyl group,

with a saturated solution of a hydrohalic acid at an elevated temperature

or, when R_4' represents a benzyl group, with catalytically activated hydrogen and, when required, converting a free carboxylic acid thus obtained into a pharmaceutically acceptable salt thereof with a base.

12. Process for the production of compounds having the formula I as defined in claim 1 but wherein R_2 may not represent a hydrogen atom and their pharmaceutically acceptable salts with bases which comprises reacting a compound having the formula VII

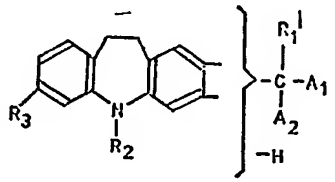


(VII)

wherein R_1 and R_3 have the meanings given in claim 1 with a reactive ester of a lower alkanol having at most 4 carbon atoms, and, when required, converting a free carboxylic acid thus obtained into a pharmaceutically acceptable salt thereof with a base.

13. Process for the production of compounds having the formula I as defined in claim 1, but wherein R_1 may represent an

alkyl group having at most 3 carbon atoms only and their pharmaceutically acceptable acid addition salts with bases, which comprises reacting a compound having the formula VIII



(VIII)

wherein R_1' represents an alkyl group having at most 3 carbon atoms

A_1 represents a lower alkoxycarbonyl group (—CO—O—alkyl) having at most 6 carbon atoms, or a cyano group, and

A_2 represents a lower alkoxycarbonyl group having at most 6 carbon atoms, a lower alkoxalyl group (—CO—CO—O—alkyl) group having at most 7 carbon atoms or a cyano or acetyl group, and

R_2 and R_3 have the meaning given in claim 1

with an alkali metal hydroxide in an organic or organic-aqueous medium or, when neither A_1 nor A_2 represents a cyano group, with an alkali metal alkanolate in an anhydrous medium or, when A_2 does not represent an acetyl group, with a mineral acid in an organic aqueous medium, liberating the free dicarboxylic acid from any salt thereof obtained on use of an alkali metal hydroxide and heating said dicarboxylic acid until the equimolar amount of carbon dioxide or carbon monoxide has been split off, and, when required, liberating the free carboxylic acid from a salt thereof with a base thus produced, and/or converting a free carboxylic acid or a salt thereof with a base thus obtained into, or into another, pharmaceutically acceptable salt thereof with a base.

14. A compound having the formula I as defined in claim 1 or a pharmaceutically acceptable salt thereof with a base whenever prepared by a process as claimed in any one of claims 7 to 12.

15. A compound having the formula 1 as defined in claim 1 or a pharmaceutically acceptable salt thereof with a base whenever prepared by a process as claimed in claim 13.

16. Process for the production of a compound having the formula I as defined in claim 1 or pharmaceutically acceptable salt thereof with a base, substantially as hereinbefore described with reference to any one of the Examples 1 to 18.

17. Process for the production of a compound having the formula I as defined in claim 1 or pharmaceutically acceptable salt thereof with a base, substantially as hereinbefore described with reference to Example 19 or 20.

18. A compound having the formula I as defined in claim 1 or a pharmaceutically acceptable salt thereof with a base substantially as hereinbefore described with reference to any one of the Examples 1 to 18.

19. A compound having the formula as defined in claim 1 or a pharmaceutically acceptable salt thereof with a base substantially as hereinbefore described with reference to Example 19 or 20.

20. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 6, 14 and 18 or a pharmaceutically acceptable salt thereof with a base together with a pharmaceutically acceptable diluent or carrier therefor.

21. A pharmaceutical composition comprising a compound as claimed in claim 15 or 18 or a pharmaceutically acceptable salt thereof with a base together with a pharmaceutically acceptable diluent or carrier therefor.

22. A pharmaceutical composition as claimed in claim 20 substantially as hereinbefore described with reference to the foregoing prescription a or b.

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